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INTRODUCTION

INTRODUCTION

Normal fetal growth is an important component of a healthy pregnancy and influences the long term health of the offspring. Intra Uterine Fetal growth restriction [IUGR], previously known as Intrauterine Growth Retardation is defined as a rate of fetal growth that is less than normal for the growth potential of the fetus, for that particular gestational age. The fetus with IUGR fails to attain its genetically determined potential size.

The definition of IUGR usually refers to fetuses whose estimated birth weight is below the 10th percentile for its gestational age, whose abdominal circumference is below the 2.5th percentile (or) those whose birth weight at term is less than 2,500 grams. While 80-85% of these fetuses are constitutionally small but healthy, 10-15% are true IUGR and the remaining 5-10% are affected by chromosomal or structural anomalies.¹ The fetal weight is determined by the genetic growth potential, health of the fetus and the capacity of the mother to supply adequate nutrients required through the placenta.

The etiology of fetal growth restriction can be due to maternal, fetal or placental causes. Some of the most frequent maternal causes are Diabetes and Hypertension while fetal causes are congenital anomalies or genetic predisposition. But the most significant and frequent cause is

utero placental insufficiency. Due to the utero placental vascular maladaptation of the placenta there is increased vascular resistance in the placental bed and transfer of substrates across the uteroplacental membrane is affected causing fetal growth restriction.

EPIDEMIOLOGY:

Worldwide IUGR is observed in about 3-10% of pregnancies every year. 24 % of newborns born every year are found to be growth restricted.² Asia accounts for more than 75% of all affected infants [2011].¹ The incidence of IUGR varies from region to region. The prevalence of IUGR is 10% of all pregnancies and 25% of high risk pregnancies. In India, according to UNICEF [2001] surveys, the incidence of IUGR is about 25-30 %. The perinatal mortality rate is 4-8 times higher for growth retarded infants and morbidity is noted in 50% of surviving infants.³

The study of the natural history of IUGR has many challenges as growth failure is often not detected antenatally during a routine clinical check up and up to a third of IUGR fetuses go unrecognized before delivery.

SEQUELAE OF IUGR

IUGR is associated with an increased risk of perinatal mortality and morbidity.

It is vital to identify IUGR babies antenatally since maternal complications like Pre eclampsia; placenta abruptio, and still birth ^{4,5} are common during pregnancy. Postnatal, IUGR babies are associated with neonatal morbidity and mortality. Perinatal morbidity is higher due to higher incidence of associated complications like meconium aspiration, hypoglycemia, hyaline membrane disease, sepsis and intra partum asphyxia. As adults, they are at risk of developing adult onset Diabetes, Hypertension,⁶ Cardiovascular diseases as well as emotional, behavioural, social problems and impaired neurological development.

The correct diagnosis of IUGR fetuses will allow for a planned delivery at a tertiary care center and a safe delivery, which is the main objective of antenatal care. Early detection puts the clinician and mother at an advantage to choose the optimal time of delivery, to supplement the nutritional status of the mother and to improve the transfer of nutrients across the placental bed via vasodilators or anti thrombotic drugs.⁷

As a large proportion of IUGR is due to placental insufficiency the study of the placenta by imaging modalities will provide a clue to differentiate between normal and IUGR fetuses.⁸

Ultrasound assessment of placenta is usually limited to, assessment of the location; maturity and presence of sub chorionic hemorrhage. Volumetric assessment of the placenta by 2D and 3D images is limited by the narrow field of view in ultrasound. Years of research on Ultrasound evaluation of the placenta in IUGR haven't been very fruitful in the prediction of IUGR. Therefore other modalities have to be brought into play to assess the placenta. Doppler is a promising modality which reflects the ongoing vascular compromise of the placenta. However, it offers a study of the effects of IUGR rather than an actual study of the placenta per se. MRI with its large field of view, absence of ionising Radiation and good spatial resolution is an ideal tool to assess the placenta.

Fetal MRI is recently used as an adjunct to ultrasound to diagnose fetal congenital anomalies. Previously assessment of placenta by MRI has been limited to assessment of location or presence of myometrial invasion in Placenta Accreta. Recently interest has been generated in directly assessing the placenta in IUGR.

Few studies have been published regarding the placental phenotype and signal intensity measurements in normal and IUGR placenta. However, there is a lacuna regarding placental intensity measurements related to gestational age of the fetus. As the placenta is an ever changing

organ, growing with the fetus, hypothetically the signal intensity should also vary related to the gestational age of the fetus. Also correlation of placental MR imaging with morbidity and mortality hasn't been attempted so far in published data.

This study was undertaken to bridge this lacuna in knowledge and also due to the high socio economic relevance of IUGR which has a high incidence in the low socio economic group in India.

AIMS AND OBJECTIVES

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PRIMARY AIM:

To assess and compare the role of Placental MRI and Placental Doppler as a predictor of Perinatal morbidity or mortality in Intrauterine Growth Restriction.

SECONDARY OBJECTIVES.

1. To derive placental, Amniotic fluid and fetal liver signal intensity ratios and correlate it with perinatal morbidity and mortality in IUGR fetuses.
2. To compare these ratios with already established criteria of Umbilical artery and Middle cerebral arterial Doppler.
3. To test the hypothesis that placental signal intensity ratios will be useful as a predictor of placental insufficiency.

REVIEW OF LITERATURE:

REVIEW OF LITERATURE

Every fetus has an inherent growth potential to reach a predetermined fetal weight in a favorable environment. But human pregnancy can be affected by conditions that restrict the normal growth of the fetus in utero leading to Intrauterine Growth Restriction [IUGR]. Although IUGR is an adaptive response by the fetus to low nutrient availability it is associated with significant morbidity and mortality.

The definition of Small for Gestational Age refers to fetuses whose estimated birth weight is below the 10th percentile for its gestational age, whose abdominal circumference is below the 25th percentile or whose birth weight at term is less than 2500 gms. While 70 % of these fetuses are constitutionally small, in 30% the cause is pathological. There is continuing debate as to whether the 10th or 5th percentile should be taken as a cutoff value for designation. Research has proved that solely depending on estimated fetal weight to identify IUGR is unreliable and Jua Zhang et al ⁸ concludes that an ideal definition of IUGR should take into account the growth potential of the fetus, fetal size and placental health. They suggest an integrated diagnosis with multiple modalities as a promising concept to differentiate small for Gestational age [SGA] fetuses from at risk IUGR fetuses.

DEVELOPMENT OF PLACENTA

A basic knowledge of the development of the placenta [Table 1] is vital to understand the pathology in IUGR placentas.

TABLE 1- FORMATION OF PLACENTA

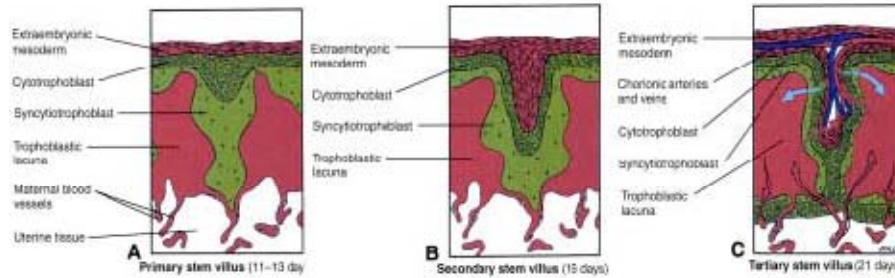
Gestational age /days	Stage of placental formation.
4-5	Blastocyst reaches uterine lumen
5-6	Apposition of blasto cyst
7	Adhesion
9	Lacunae formation in syncytiotrophoblast
11-13	Primary stem villi
14-	Cytotrophoblast cells occlude spiral arteries. Maternal Plasma enters intervillous spaces.
16	Secondary villi
21	Tertiary villi-fetal vessels enter
8 weeks	End of embryonic period
12 weeks	Maternal whole blood enters intervillous spaces of placenta.

The future embryo develops from the blastocyst, which is formed from the zona Pellucida on day 5-6 post fertilization. The first step in formation of placenta is implantation. This occurs due to apposition, adhesion and invasion.⁹ As the embryo is embedded within endometrium the type of implantation is called interstitial. The developing blastocyst with its cytotrophoblast and syncytiotrophoblast layer approaches the uterine wall at its site of implantation. At site of chosen apposition the

adhesion of blastocyst occurs followed by invasion. Invasion is by burrowing syncytiotrophoblast which invades the basal lamina of the uterine endometrium. Once invasion occurs, the utero placental circulation is formed in several steps. The invading embryo is initially nourished by the secretions from the endometrial glands.

UTEROPLACENTAL CIRCULATION: [Table1] There are several stages in the formation of the uteroplacental circulation. The first association takes place around day 9 when the invading syncytiotrophoblast develops lacunae which anastomose with blood filled sinusoidal spaces in the endometrium. The Cytotrophoblast layer beneath the syncytial trophoblast forms finger like projections called villi that project into these vascular spaces. The villi thus formed with syncytial trophoblast covering the cytotrophoblast is known as the primary villi.⁹ By the end of the second week the extra embryonic mesenchyme invades the core of the villi to form secondary villi. By the third week the fetal blood and circulatory systems are forming. By day 21 the embryonic blood vessels enter the mesenchyme of the villi and transform the secondary into tertiary villi. [Fig 1]. At this point the fundamentals of the villus circulation are in place. The fully developed placenta is a combination of a fetal portion - the chorion and the maternal portion formed by the decidua. In its final form the placenta is made up of stem

FIG -1. DEVELOPMENT OF THE HUMAN PLACENTA



Formation of the chorionic villi.

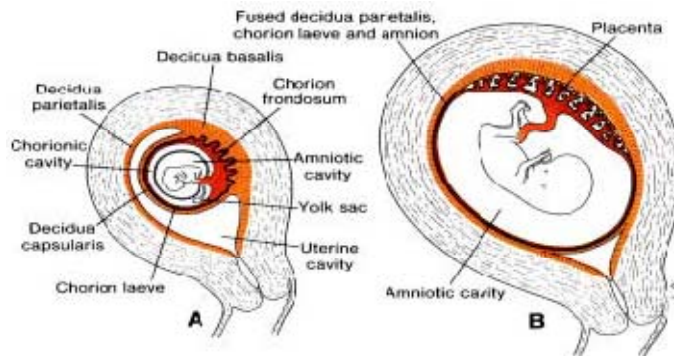
A. Primary stem appear on days 11-13 as cytotrophoblastic proliferations bud into the overlying syncytiotrophoblast.

B. By day 16 secondary villi are formed as the extraembryonic mesoderm (mesenchyme) invades the center of the villi.

C. By day 21 fetal blood vessels appear within the villi, forming tertiary villi. The intervillous space contains maternal blood plasma.

Larsen, WI, Human Embryology, 3rd ed., Churchill Livingstone, New York (2001).

FIG 2- THE DECIDUA AND PLACENTA.



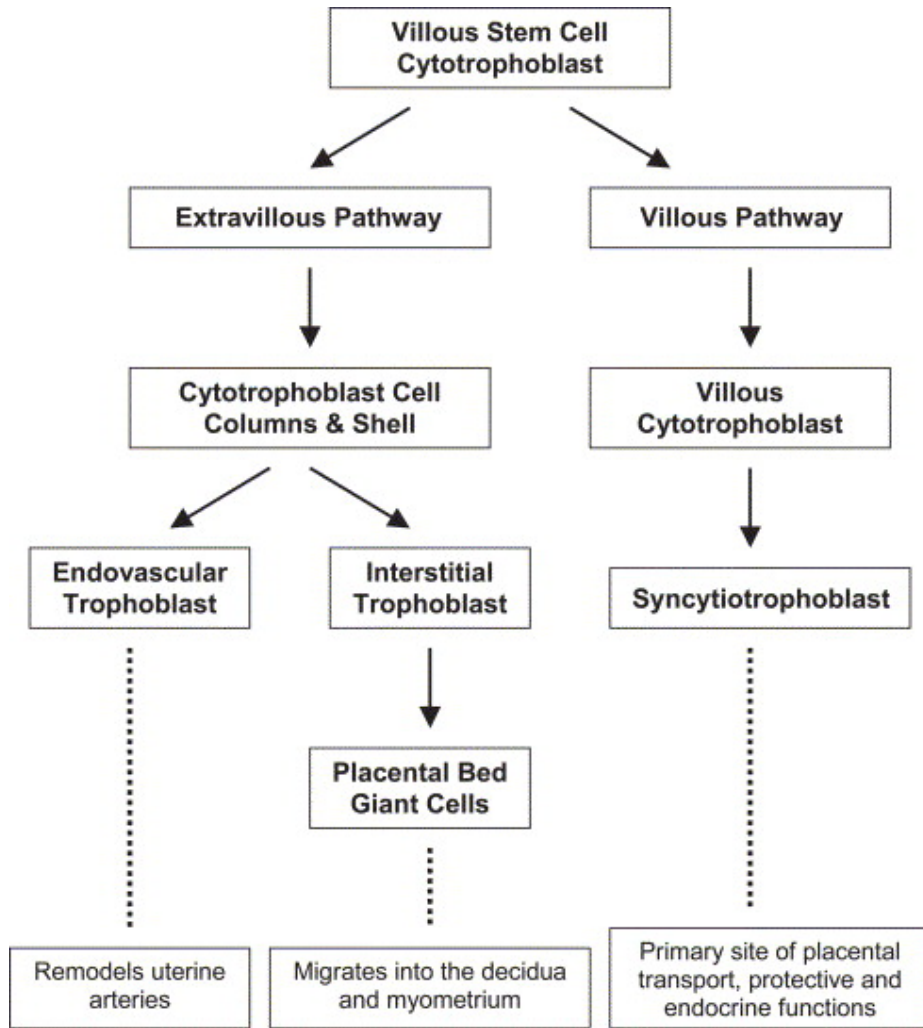
The decidua and fetal membranes.

A., the end of the 2nd month and

B., the end of the 3rd month.

Langman's Medical Embryology 8th ed., Lippincott, Williams & Wilkins, Philadelphia (2000).

FIG: 3 FUNCTIONS OF THE CYTOTROPHOBLAST



villi that extend from the chorionic plate. These villi float in the intervillous [maternal blood space] as terminal villi or attach to the decidua basalis as anchoring villi. [Fig-2]

During the first trimester of pregnancy the cytotrophoblast partially occludes the uterine vessels,[Fig 3] thus the villous spaces are filled only with maternal plasma. This provides a low oxygen environment for organogenesis in the developing embryo. Later the occlusion is recanalised and maternal blood fills the intervillous spaces. The cytotrophoblast also replaces the endothelium and smooth muscle of the endometrial spiral arteries thus releasing these arteries from maternal influences and forming a low resistance vascular bed for adequate fetal nourishment. The highly branched tertiary villi allow for exchange of nutrients across a layer formed of embryonic syncytium and cytotrophoblast. As spiral arteries lack maternal endothelium and the smooth muscle in their walls has been altered, they do not respond to hormonal or neural signals from the mother thus ensuring a steady supply of blood and nutrients to the growing fetus.

In its final form the fetus hangs suspended in the amniotic cavity by the Umbilical cord. The cord inserts into the chorionic plate which in turn is anchored into the decidua basalis. On the maternal side during the fourth and fifth month the decidua develops septa that incompletely

divide the intervillous space. The resulting placenta is made up of a group of villi [cotyledons] that are partially separated from each other.

The fully formed placenta is hemochorial in nature because maternal blood in the intervillous space is separated from the fetal blood in the vessels within the villi only by elements of the chorion. The chorionic barrier is composed of syncytiotrophoblast, cytotrophoblast, basal lamina, fetal mesenchyme, basal lamina of the fetal capillary and the endothelium of the fetal capillary. By the fourth month the barrier is further thinned by diminishing cytotrophoblast which almost completely disappears. This facilitates the rapid exchange of nutrients.

As pregnancy progresses the villi undergo maturation. The diameter of the villi decreases while their spaces become sinusoidal, dilated and eventually occupy the whole of the cross section of the villi.¹⁰ Simultaneously the villous syncytiotrophoblast overlying areas of the fetal capillary thin out to form vascular-syncytial membranes.¹⁰ These are specialized areas for the function of gas transfer across the placenta.

PLACENTAL FETAL RELATIONSHIP:

Named for its appearance [Geek word plakuos meaning flat cake] the placenta is a surrogate respiratory, excretory and digestive organ for the growing fetus. The human placenta is haemochorial: fetal blood flows

through villi which are separated from maternal blood flowing through intervillous spaces. The placenta consists of both fetal and maternal components. The villi of the chorion frondosum are fetal in origin supplied by the Umbilical artery and protrude into the intervillous spaces bathed in blood from the maternal uterine artery. The Decidua placentalis lining the intervillous space forms the maternal component.

Placental dysfunction occurs in many disorders of pregnancy like IUGR and Pre eclampsia making the study of the placenta an increasingly important issue in obstetrics. Early developmental abnormalities in the placental bed and villi can cause ischemia or thrombosis in the placental bed that can result in IUGR, placental separation, or hypertension with increased morbidity or mortality to the growing fetus.

The placenta is often overlooked during routine evaluation in a normal gestation, receiving attention only when an abnormality is suspected. The relationship between fetus and placental circulation is crucial for transfer of essential nutrients from placenta to fetus. Maturation changes are taking place in the placenta throughout pregnancy. In normal pregnancies the uptake of glucose and oxygen by the placenta exceeds that of the fetus in mid pregnancy. The fetal growth, however exceeds placental growth by the third trimester. Small for

gestational age [SGA] infants have smaller placentas and a reduced placental to fetal weight ratio than normal fetuses.¹¹

An impairment in trophoblast invasion of maternal decidua has been hypothesized as the cause for the insufficient transformation of the maternal uterine spiral arteries into low resistance vascular bed of the placenta. This results in high placental vascular resistance and therefore reduced placental flow, which is reflected in the spectral waveforms obtained from the Uterine arteries and Umbilical arteries.

PATHOPHYSIOLOGY

To identify IUGR fetuses early we require knowledge of etiology, pathophysiology and natural history. The many causes of IUGR are summarized in Table 2. Structural Fetal abnormalities can be identified by ultrasound imaging. Maternal causes can be diagnosed via biochemical investigations or proper history. The remaining category with placental vascular disturbances is a challenge to identify prenatally.

TABLE 2: Causes of Intrauterine Growth Restriction.

FETAL	MATERNAL [25-35%]	PLACENTAL
Chromosomal disorders. Genetic Syndromes. Multifactorial congenital malformations. Congenital viral infections.	Chronic or pregnancy induced hypertension. Diabetes . Sickle cell disease. Renovascular disease. Thrombophilias. Poor Nutrition. Smoking, drug or Alcohol abuse.	Utero Placental insufficiency. Structural malformations of the placenta.

Adequate fetal growth is dependent on nutrient supply through the placenta. Glucose and amino acids are actively transported. The glucose / insulin/insulin like growth factor plays a major role in tissue specific growth regulation. Approximately 70% of glucose and 45% of oxygen are used by the placenta itself, adequate nutrient supply to the fetus is dependent on uterine perfusion, fetoplacental gas exchange and high oxygen affinity of fetal hemoglobin.¹² In normal placentas there are significant changes taking place in the vascular bed to accommodate accelerating fetal growth. With the successful trophoblast invasion the spiral arteries are invaded and turned into a low resistance high capacity vascular bed. Consequently, as gestation advances the proportion of cardiac output to the placenta increases and reaches about 500-600 ml/mt at term. This is matched by an increase in villus capillary surface and decreased umbilical vascular resistance on the fetal side. The fetal cardiac function increases to match this increased flow and there is almost a five to ten fold increase in umbilical artery flow and venous flow to maintain a constant blood flow volume /kg fetal body weight throughout gestation.

Distribution of nutrients entering the fetal circulation via the Umbilical vein to the vital organs depends on the unique dynamics of the fetal circulation. Venous shunting at ductus venosus distributes nutrients to the liver and heart. At the next level the right atrium shunting directs

nutrient rich blood to the heart and the brain while venous return is directed towards placenta. In an IUGR fetus utero placental insufficiency occurs at many levels like nutrient delivery, placental uptake and distribution within the fetus.

Placental pathology in IUGR

The functional unit of the placenta is the terminal villi. [Fig 4] IUGR placentas with insufficient function must have either a reduced number of villi, or normal number with reduced function.¹⁰ Placental infarcts cause a reduction in number,¹⁰ while perivillous fibrin deposition [Fig 5] and fetal artery thrombosis result in impaired functioning of villi.¹⁰ The placenta has a great functional reserve and can compensate for up to 30% loss of villi. Of the three pathologies affecting the IUGR placenta it is the infarct that is most devastating. Placental infarcts are mainly caused by Retro placental hematomas or maternal artery thrombosis. Of these placental hematomas are rare in IUGR fetuses and the main cause is maternal artery thrombosis.

INTRA UTERINE GROWTH RESTRICTION IDENTIFICATION

Intrauterine growth restriction is defined as a fetus with an estimated weight below the 10th percentile for gestational age. As not all fetuses below the 10th percentile are at risk for adverse outcomes many

FIG: 4. THE STRUCTURE OF NORMAL PLACENTAL VILLI

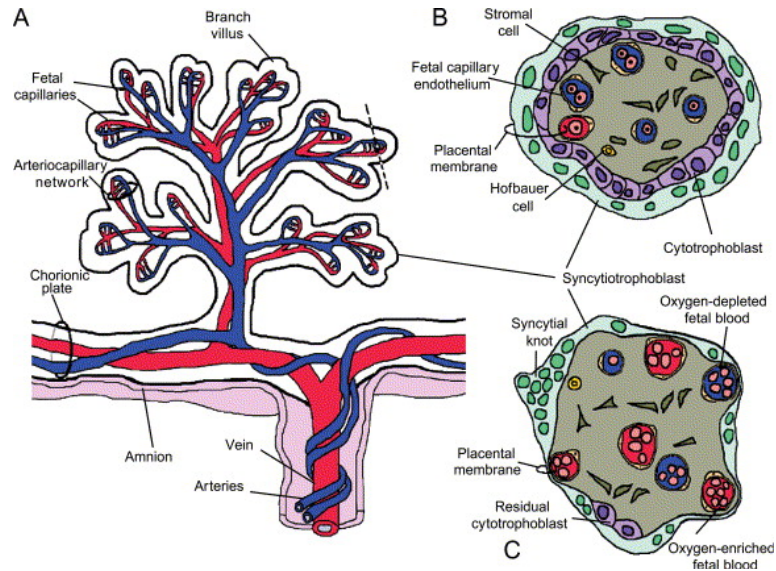
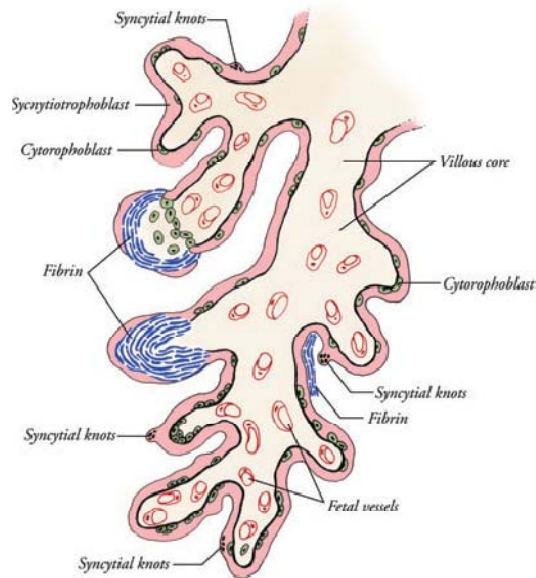


FIG: 5: STRUCTURAL CHANGES IN VILLUS OF IUGR PLACENTA



Absence of endovascular trophoblast invasion of myometrial segments of the spiral arterioles, characteristic of IUGR, avails a high resistance vasculature with a persistent smooth muscle histology in the maternal spiral arterioles. This lack of transformation predisposes to hypoperfusion, hypoxia, re-perfusion injury, oxidative stress and, ultimately, to signs of villous tree maldevelopment in the second half of the pregnancy, all factors associated with IUGR.

authors have used different cut offs, including less than 3rd percentile or 5th percentile of estimated weight. Of those identified as less than 10th percentile of estimated fetal weight in utero, 70% will be constitutionally small and only 30% will be at risk for poor neonatal outcomes. On the other hand, some fetuses with estimated weights above the 10th percentile demonstrate characteristics of fetal growth restriction revealing the limitations of this definition of IUGR.

CLASSIFICATION OF IUGR.

IUGR can be classified under many headings.

A] Based on Fetal Biometry:

It is usually classified as two types based on the Head circumference / abdominal circumference [HC/AC] ratio. Normal HC/AC ratio ranges between 87 -106. Symmetric IUGR is a symmetrical reduction in fetal measurements of the body and head, due to insult, to growth occurring early in the second trimester. Here the HC /AC ratio is within normal limits.

An elevated HC/AC ratio indicates smaller abdominal circumference as compared to head circumference and denotes Asymmetric IUGR. Asymmetrical IUGR is due to restriction to normal

growth occurring later in gestation and is due to utero-placental insufficiency. The pathologic process is extrinsic to the fetus.

Approximately 20-30% are symmetrically small with growth restriction affecting all biometric measurements: i.e. skeletal, head and abdomen. It is thought to have an early onset condition. Symmetric IUGR is associated with conditions that reduce the absolute number of fetal cells like aneuploidy or early congenital infections. Asymmetrical IUGR forms 70-80% of IUGR fetuses, and is believed to have a late onset with relative sparing of skeletal and head measurements but a decreased abdominal circumference. This reflects less glycogen storage, diminished liver size and reduced subcutaneous fat. Asymmetric IUGR is associated with in utero placental insufficiency and is accompanied by a redistribution of fetal blood to vital organs and a reduction in fetal growth rather than number of cells. Unfortunately, this distinction between symmetrical and asymmetrical IUGR is not clear and shows lot of overlap. The gestational age at which the IUGR sets in is more important than the nature of the risk factor itself.

B] *Based on the time of onset:*

IUGR can also be classified as early or late onset with cut off as 34 weeks.

Early onset IUGR:

Intrauterine growth restriction can have an early onset before 34 weeks or late onset. Early growth restriction is defined as detection of restricted fetal growth that results in either death of the fetus or delivery on maternal or fetal grounds before 34 weeks of gestation. Severe early onset IUGR may be associated with aneuploidy like triploidy, trisomy 18 etc. Other causes include maternal causes like hypertension, eclampsia and placental insufficiency.

TABLE 3: ULTRASOUND FEATURES OF EARLY ONSET SEVERE IUGR AT 28 WEEKS OF GESTATION

PARAMETER	FINDINGS
Biometry	Estimated fetal weight <10th percentile. [< 640 gms] Head/ abdomen circumference [HC/AC] ratio 1.35.[normal < 1.20] Amniotic fluid index [AFI]7 cm. Normal 10-20 cm,
Doppler	UTA- Bilateral early diastolic notches. Right UTA PI 1.65.Left UTA PI- 1.97. UA -AEDV. MCA- PI 1.12 [redistribution]
Biophysical score	8/8 normal.
Anatomy	Short femurs. Mildly echogenic bowel

UTA	-	Uterine arteries
UA	-	Umbilical Arteries.
MCA	-	Middle cerebral arteries.
HC/AC	-	Head circumference /Abdomen circumference ratio of fetus
AFI	-	Amniotic Fluid Index.
AEDV	-	Absent End Diastolic Flow
PI	-	Pulsatility index

Typical Ultrasound findings in early onset are given in Table 3. Elevated HC/AC ratios indicate asymmetrical IUGR with brain sparing. The Utero placental insufficiency is depicted by abnormal Uterine Artery [UTA] and Umbilical Artery [UA] Doppler findings. Redistribution of cerebral blood flow as depicted by MCA tracings and reduced Amniotic Fluid are relevant to fetal adaptation to Uteroplacental insufficiency. Mothers are usually at high risk of coexistent preeclampsia. While UTA Doppler and Placental morphology are valuable in diagnosing IUGR, it is the Umbilical artery and MCA along with Ductus venosus and Biophysical Profile testing , that are relevant for management of the early IUGR fetus.

A number of randomized trials have concluded that no Doppler parameter is useful as a screening tool for early onset IUGR in low risk unselected groups. However, screening for early onset IUGR can be done by Uterine artery Doppler at 18-22 weeks in high risk mothers with pre eclampsia. A mean PI value > 1.45 had a sensitivity of over 70% for the detection of IUGR and delivery before 34 weeks.¹³ Bilateral notching also gives similar results, but is confounded if the placental insertion is confined to one side of the uterus when the ipsilateral UTA waveform has more significance than contralateral waveform. UA Doppler and MCA

studies, though not useful as a screening tool for IUGR are helpful to recognize fetuses at risk for Perinatal morbidity and mortality.

The overall strategy in management is to delay delivery under intensive fetal monitoring. Fetal ultrasound monitoring is by UA Doppler and Amniotic fluid volume estimation. The time interval between Doppler monitoring depends on individual fetuses and may vary from once /week to daily monitoring as required. Administration of steroids has also been recommended to improve fetal lung maturity prior to delivery in these patients.

LATE ONSET IUGR:

Beyond 34 weeks the diagnosis of late onset IUGR is established by findings of asymmetry [Increased HC/AC ratio], abnormal uterine artery Doppler [UTA] and Middle Cerebral artery [MCA] redistribution as depicted by PI values less than 1.0. The value of UA Doppler is less in this group as it is uncommon to find an absent or reversed End Diastolic flow in these mothers. Oligo hydramnios is prevalent in this subset unlike in early onset. Patients can be given a trial vaginal delivery under continuous fetal heart rate monitoring, although fetal distress and meconium staining during labor can occur. Good Perinatal outcome is expected even with early delivery.

A subset of patients with fetal weight less than 10th percentile are symmetrically small [normal HC/AC ratio], with normal MCA Doppler, adequate amniotic fluid and normal appearance of placenta. These are healthy constitutionally small normal fetuses and may be allowed to go on to spontaneous delivery at term.

IMAGING IN IUGR

ULTRASOUND

The placenta has been the focus of obstetric ultrasound since 1973. The placental length is approximately six times the placental width at 16- 20 weeks.¹⁴ Placental thickness more than 4 cm before 26 weeks is abnormal. Pathological causes of increased placental thickness include Ischemic -thrombotic damage, Intraplacental Hemorrhage, Placental tumors like chorioangioma and fetal hydrops. Placental lakes occur in 5% of pregnancies and represent intervillous spaces without villous trees. Slow venous flow signals may be seen within. These spaces, change shape with uterine contractions. Though considered a normal finding, multiple lakes with the decreased umbilical artery flow has been associated with IUGR.¹⁴ Mild pre eclampsia is more common in these patients though the outcome is generally good.

Thrombosis of the placenta has two appearances on ultrasound. The first is an irregular created cystic lesion in the center of the echogenic cotyledons with a hyper echoic thick rim. These lesions termed Echogenic cystic lesions [Fig 6] are more frequently visualized in pregnancies with high risk of third trimester complications. The hyper echoic rim is thought to represent necrotic villi aggregated in maternal blood. Color flow is negligible in these lesions unlike in placental lakes. The second lesion is infarction of the whole villous tree .On ultrasound they appear as echogenic triangular areas [Fig 7] and represent necrotic under perfused villi. Peripheral infarcts are of less importance than central infarcts as most functioning villi are present in the center of the placenta.

Ultrasound Grading of placenta [Fig 8] was used originally as a predictor of fetal lung maturity.¹⁵ Later it was discovered that placental grading was associated with normal maturation and that there was no relationship between Grade III placenta and IUGR.¹⁶ Jean Proud et al in 1987 studied 2000 subjects and concluded that early placental maturation [Grade 3 before 34-36 weeks] was associated with problems in labor and low birth weight. But they also reported that the sensitivity was low, indicating that only a few of these babies with Perinatal problems would show the early maturation of placenta.¹⁷

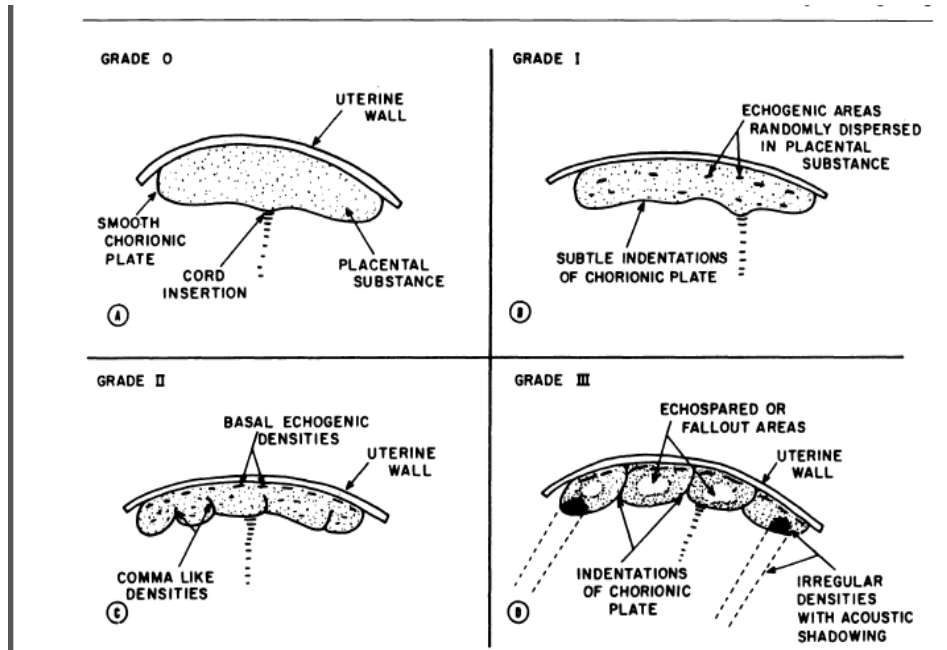
FIG 6 - ECHOGENIC CYSTIC LESIONS [ECL] BY ULTRASOUND REPRESENTING INTERVILLOUS THROMBOSIS



FIG 7 – ECHOGENIC LESIONS BY USG SUGGESTING VILLOUS INFARCTS



FIG 8- SCHEMATIC DIAGRAM ILLUSTRATING GRANNUMS CLASSIFICATION OF PLACENTA



DOPPLER

Once grading of placenta was found to be less predictive, the focus turned towards Doppler criteria. Soon it was found that deterioration of circulatory status was progressive in IUGR fetuses.

Elevation of the Uterine artery pulsatility index or persistence of early diastolic notch after 22 weeks is evidence of abnormal placental development due to abnormal trophoblast invasion and placental infarcts.¹⁸

The Umbilical artery abnormal indices preceded changes in Cerebro placental ratio and Middle Cerebral Artery [MCA] pulsatility indices [PI]. These changes were categorized into early and late stage changes by Ferrazzi et al.¹⁹ Absent End diastolic flow [AEDV] in Umbilical artery and MCA artery abnormal flow was detected 2-3 weeks prior to changes in Fetal Heart Tracing [FHR]. Venous changes in Ductus venosus and IVC [Inferior Vena Cava] waveform abnormalities occurred later, just a few days prior to abnormal FHR.

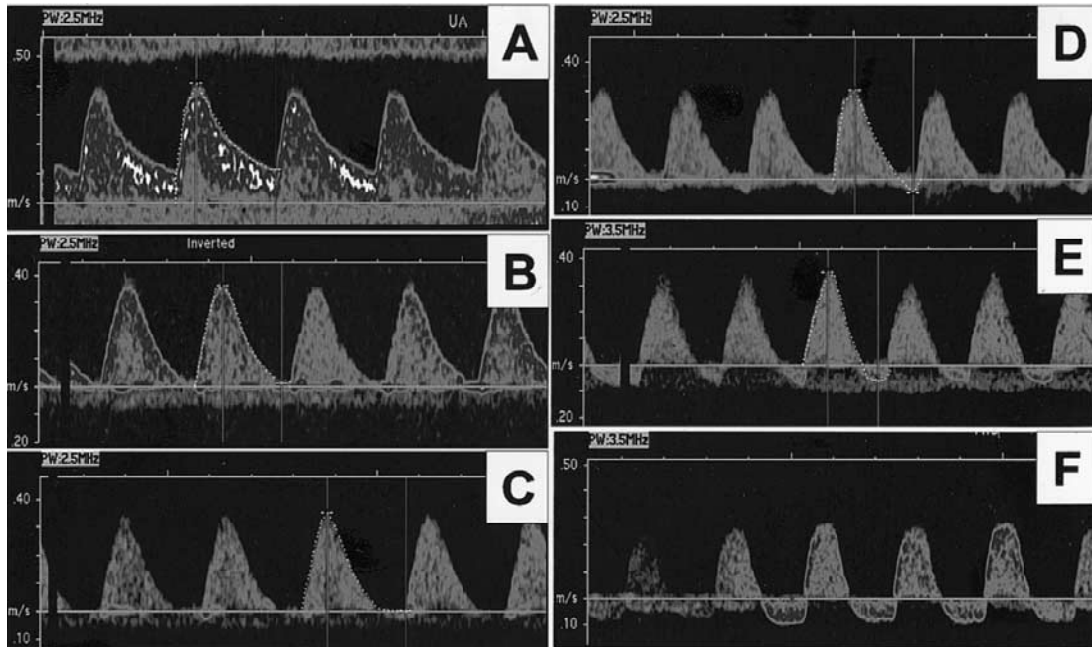
The developing embryo is connected to the placenta by the umbilical cord. Flow can be detected in the cord from around 10 weeks of gestation. During the first trimester the Umbilical artery [UA] waveform is characterized by Absent End Diastolic [AEDV] flow. As pregnancy

advances the Diastolic flow increases and PI [Pulsatility index] progressively falls [FIG 9]. Absent end Diastolic flow [AEDV] in the UA by 18- 22 weeks is an abnormal finding. The PI values decline from 2.0 in early first trimester to around 1.0 at term.¹⁴

Early on the value of Umbilical artery Doppler in IUGR was established. In normal pregnancies the normal indices of S/D [Systolic /Diastolic Ratio], PI [Pulsatility index] and RI [Resistive index] of Umbilical artery decrease with advancing gestation due to increasing diastolic flow. However, in IUGR there is decreasing diastolic flow due to increased resistance in placental vascular bed and all parameters increase. With worsening placental insufficiency there is Absent End Diastolic and finally reversed End Diastolic flow noted in the Umbilical artery. Yoon et al²⁰ proved that absent UA diastolic flow is a strong predictor of adverse Perinatal outcome.

The circle of Willis can be demonstrated at the base of the fetal skull. When the head is transverse the Middle Cerebral Artery [MCA] runs vertically towards the probe and is easily visualized. The typical MCA waveform at 28-32 weeks is characterized by high systolic velocity and low diastolic velocities. [Fig 10] The PI values remain high at greater than 1.45. Low diastolic flow indicates normal auto regulatory mechanisms. When oxygen tension in blood is lowered due to various

FIGURE 9 : UMBILICAL ARTERY WAVEFORM



(A) The normal umbilical artery flow velocity waveform has marked positive end-diastolic velocity that increases in proportion to systole toward term

(B) Moderate abnormalities in the villous vascular structure raise the blood flow resistance and are associated with a decline in end-diastolic velocities. When a significant proportion of the villous vascular tree is abnormal (50%-70%), end-diastolic velocities may be

(C) absent or even

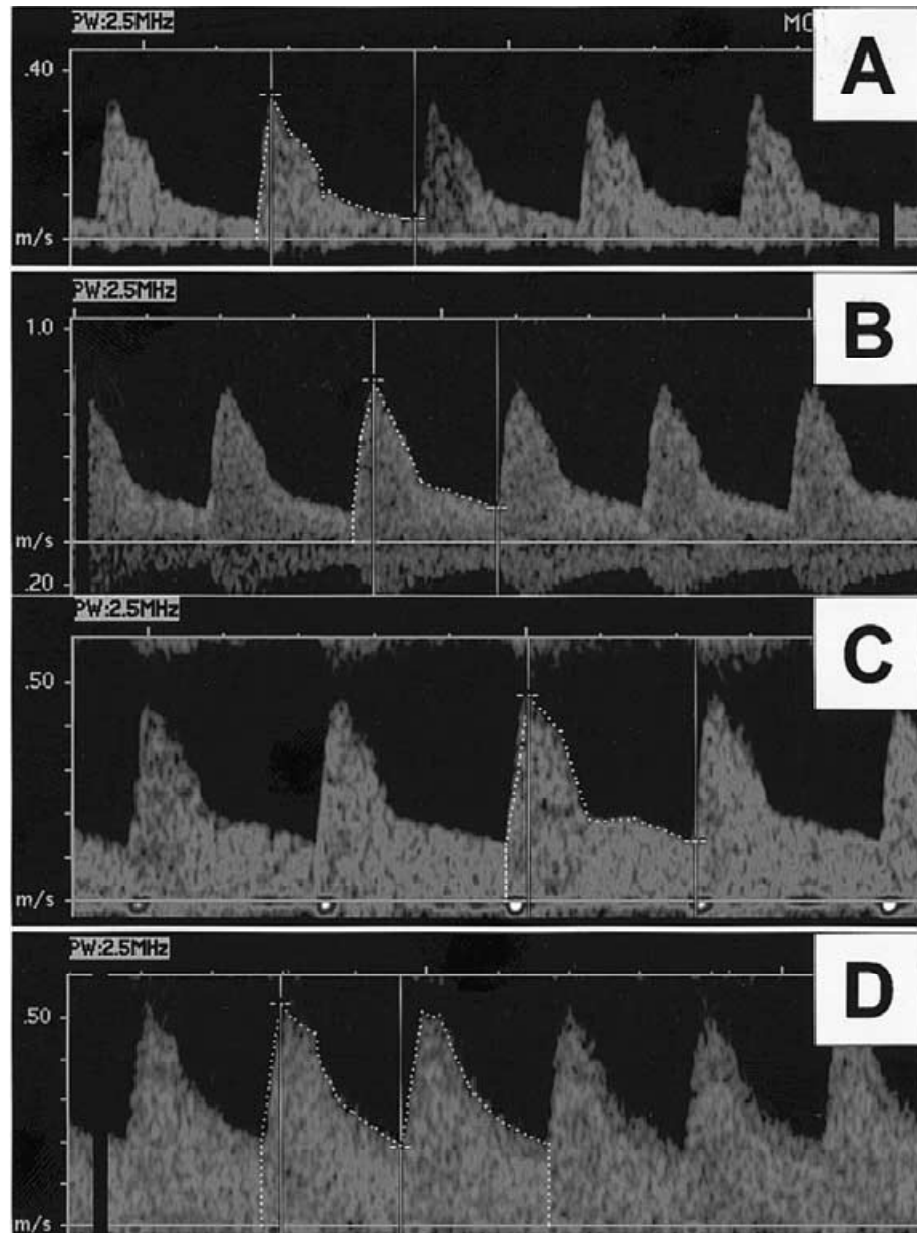
(D) reversed. Depending on the magnitude of placental blood flow resistance and the fetal cardiac function reversal of end-diastolic velocities may be (D) minimal,

(E) moderate, or

(F) severe. In the latter case, precordial venous flows were universally abnormal.

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FIG- 10 -CHANGES IN MIDDLE CEREBRAL ARTERY WAVEFORM WITH ADVANCING GESTATION



(A) The normal middle cerebral artery flow pattern has relatively little diastolic flow. With elevation of placental blood flow resistance the changes in the middle cerebral artery waveform may be subtle, although the cerebroplacental ratio may become abnormal as in fetus B. With progressive placental dysfunction there may be increase in the diastolic velocity resulting in a decrease in the Doppler index (Brain sparing, C). With marked brain sparing the systolic down slope of the waveform becomes smoother so that the waveform almost resembles that of the umbilical artery (D). *Seminars in Perinatology, Vol 28, No 1 (February), 2004: pp 67-80*

causes, the vascular tone of the MCA is reduced, resulting in an increased diastolic flow. This is known as cerebral redistribution of blood flow to the fetal brain and occurs in severe IUGR.

Fetal Middle Cerebral artery [MCA] is a low resistance circulation throughout pregnancy. In IUGR as flow decreases due to placental resistance the fetus attempts to maintain flow to vital organs like brain which is called Brain sparing effect. This causes increased diastolic flow in MCA with a decrease in PI as a reaction to hypoxia and ischemia of the cerebral circulation. Gramellini et al ¹¹ found that the Cerebro Placental ratio [CPR] of PI by MCA / PI of UA is a constant after 30 weeks and suggested a cut of value below 1 as abnormal. This ratio was found to have higher sensitivity [100%] than PI of MCA alone [50%] when correlated with Apgar Score .²¹ This contrasts with the Indian study by Lakhar ²² who concluded that MCA PI was more sensitive than CPR ratio.

Thus the value of both UA and MCA Doppler was established early on. Later studies depicted that Umbilical artery had a better correlation in early IUGR i.e. less than 34 weeks while MCA indices were more reliable in late gestation. R. Hershkovitz et al [2000] in their study²³ on 47 fetuses in late gestation demonstrated that MCA Doppler was more useful to assess morbidity of fetuses in late gestation than UA

Doppler. Pulsatility indices of MCA below the 5th percentile were taken as abnormal. Normal Doppler reference values are given in Table 4.

TABLE 4: REFERENCE RANGES FOR DOPPLER STUDIES.

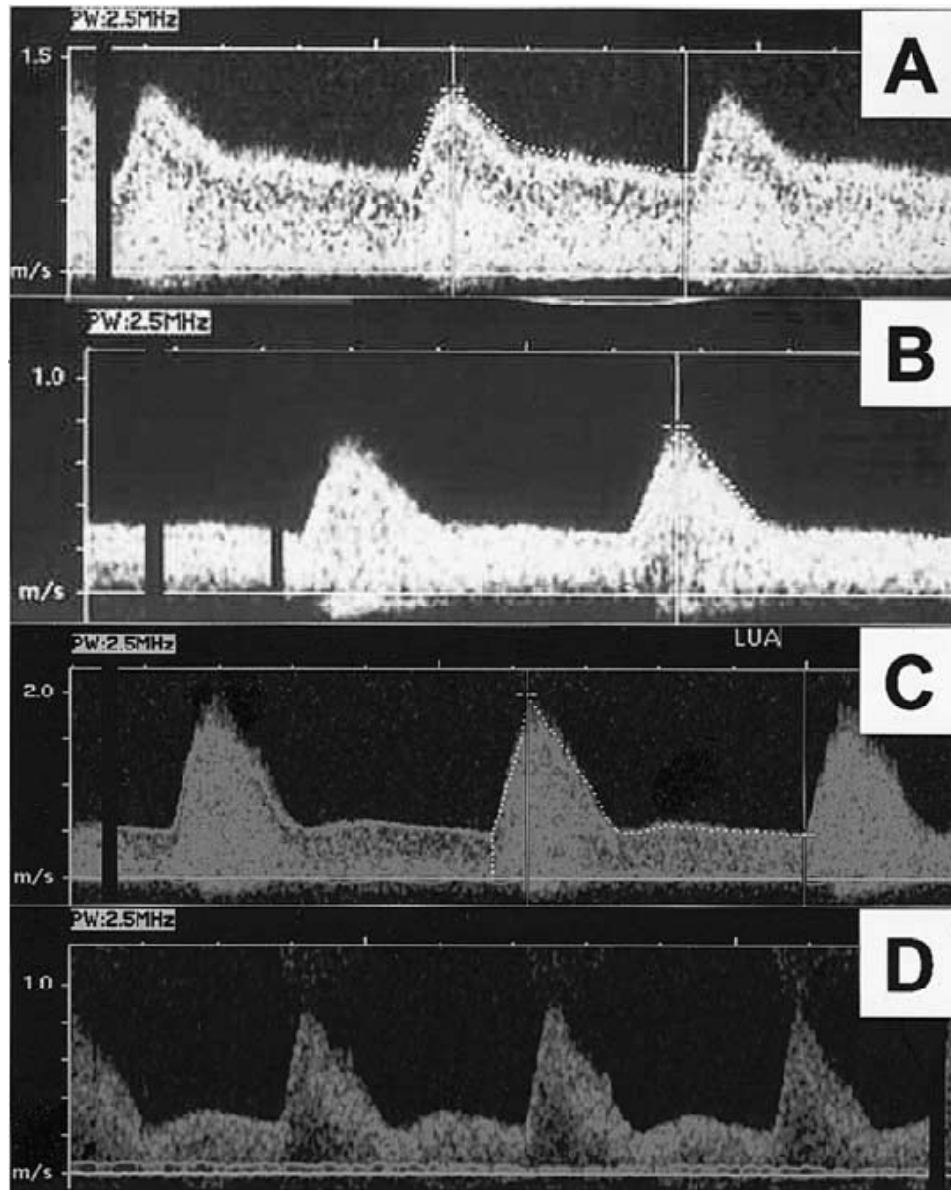
ARTERY	NORMAL PARAMETERS.
UTA- Uterine artery	Between 18-22 weeks normal UTA waveform will have no diastolic notches and a mean PI of < 1.45 High systolic velocity and increased diastolic flow.
UA-Umbilical Artery	PI values range from 2 to 1.5 in second trimester and 1.5 to 1 by term. High systolic and increased diastolic flow.
MCA-Middle Cerebral Artery	PI values are typically greater than 1.45 before term falling to 1.0 by term. High systolic with low diastolic flow.

There is a dilemma regarding differentiation of small for gestational age fetuses who are essentially normal, but fall into the category of IUGR by definition. Articles have focussed on methods to differentiate between SGA and IUGR fetuses. Gray scale parameters studied included Amniotic Fluid Volume and Grading of Placenta. Doppler of UA diastolic flow and MCA Pulsatility indices were found promising. Due to inter operator variability focus was then turned to ratios, of which the fetal Cerebro Placental Ratio [CPR] was found promising. Regarding CPR some authors based it on Pulsatility indices²⁴ of the respective arteries with a cutoff value of 1.1 under which it was deemed abnormal, while others like Grif Caterina [2013]²⁵ based it on Resistive index and established values below 1.08 as abnormal. The CPR in their study had a p value of .0001. The drawback was the low sample of IUGR fetuses [8 out of 22 SGA fetuses.] in their study.

One of the Indian studies on Doppler in IUGR was by Lakhar et al²², who in their study on the Doppler prediction of adverse Perinatal outcome in Pregnancy Induced Hypertension and IUGR, studied the role of Umbilical artery, MCA, Descending abdominal aorta [DAA] Umbilical vein and Inferior Vena Cava. [IVC] in IUGR. Using a cutoff value of Systolic /Diastolic Ratio [S/D] of MCA <11 and PI of MCA <1 as abnormal they concluded that UA S/D [abnormal if > 2 standard deviations] is the most sensitive [66.6%] and PI of MCA had both good specificity [88.2%] and Positive Predictive value [88.2] in predicting neonatal morbidity. Of the 6 mothers who showed absent or reversed end diastolic flow all had a poor outcome of Perinatal mortality.

The uterine artery forms a major branch of the Internal Iliac artery during pregnancy. It runs up by the side of the growing uterus and after entering the myometrium branches into arcuate and spiral arteries. During the first trimester the cells from the decidua migrate into the myometrium and surround the spiral arteries. They invade the arteries, denerve the spiral arteries from maternal control and replace the high resistance normal flow with a low resistance flow of passively dilated vessels. Uterine blood flow in the non pregnant state is 50ml/mt and increases to 700 ml/mt during the third trimester. Thus the early uterine artery waveform from high resistance with diastolic notch is converted to low

FIG -11- FLOW VELOCITY WAVEFORMS OBTAINED FROM THE UTERINE ARTERY BEYOND 24 WEEKS GESTATION



In the first patient (A) high volume diastolic flow is established indicating successful trophoblast invasion.

(B) Elevated placental vascular resistance is associated with a decline in diastolic velocities and a subsequent rise in the Doppler index. Persistence of an early diastolic notch in the uterine artery flow velocity waveform is evidence of increased spiral artery blood flow resistance.

(C) Frequently “notching” is more subtle beyond 32 weeks (C) than in the (D) late second or early third trimesters.

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resistance, high flow and no diastolic notch waveform by 22 weeks.[Fig -11] The Pulsatility indices at 18 - 22 weeks are usually less than 1.2. The detection of bilateral uterine artery notches with PI [Pulsatility Index] more than 1.45 is suggestive of significant uteroplacental vascular ischemia.

The role of Uterine artery also has been the subject of many studies. Megahana et al²⁶ evaluate the role of placental morphology by ultrasound and Uterine artery Doppler in predicting adverse Perinatal outcome in women with elevated Alpha Feto Protein. Abnormal placenta was described as Placental thickness more than 4 cm, abnormal texture as the presence of Echogenic cystic lesions or a jelly like appearance and Abnormal UTA [Uterine artery] Doppler as $PI > 1.45$ between 19-23 weeks of gestation. They found a significant association of UTA Doppler and prediction of IUGR. Echogenic cystic lesions are representative of placental infarcts or intervillous thrombosis. But their findings were restricted to women between 19-23 weeks of gestation and postnatal histopathology of the placenta were not studied. They conclude that the identification of abnormal placental morphology or Doppler will point out mothers who require closer monitoring.

MAGNETIC RESONANCE IMAGING.

MRI with its absence of ionizing radiation and good spatial resolution is another modality suited for antenatal imaging. The possible adverse effects of MRI on the growing fetus have been the subject of many studies with little evidence to prove any ill effects on the human fetus.^{27,28} However, it is advisable to avoid First trimester imaging by MRI when maximum differentiation occurs in the fetus,²⁹ and to defer contrast studies.

Placental imaging by MRI is relatively new, with most articles focussed on detection of Placenta Accreta and Placenta Previa. Blaicher et al in 2006³⁰ were among the earliest to study the signal intensity of normal placentas. They studied 100 normal placentas between 19-40 weeks gestational age and found that placental morphological changes with advancing gestational age, matched that of ultrasound changes. A regular homogenous placenta at 19-23 weeks, progressed to lobulated contour in later gestation and stratification of lobules after 36 weeks [Fig -12] The ratio of placenta to amniotic fluid signal intensities decreased significantly with advancing gestational age.

In 2011 Wright et al³¹ studied Placental relaxation times in Normal pregnancies and correlated these with Gestational age and analysis of morphology following delivery. They also found that T1 and T2 values

FIG - 12. GRADING OF PLACENTA BY MRI

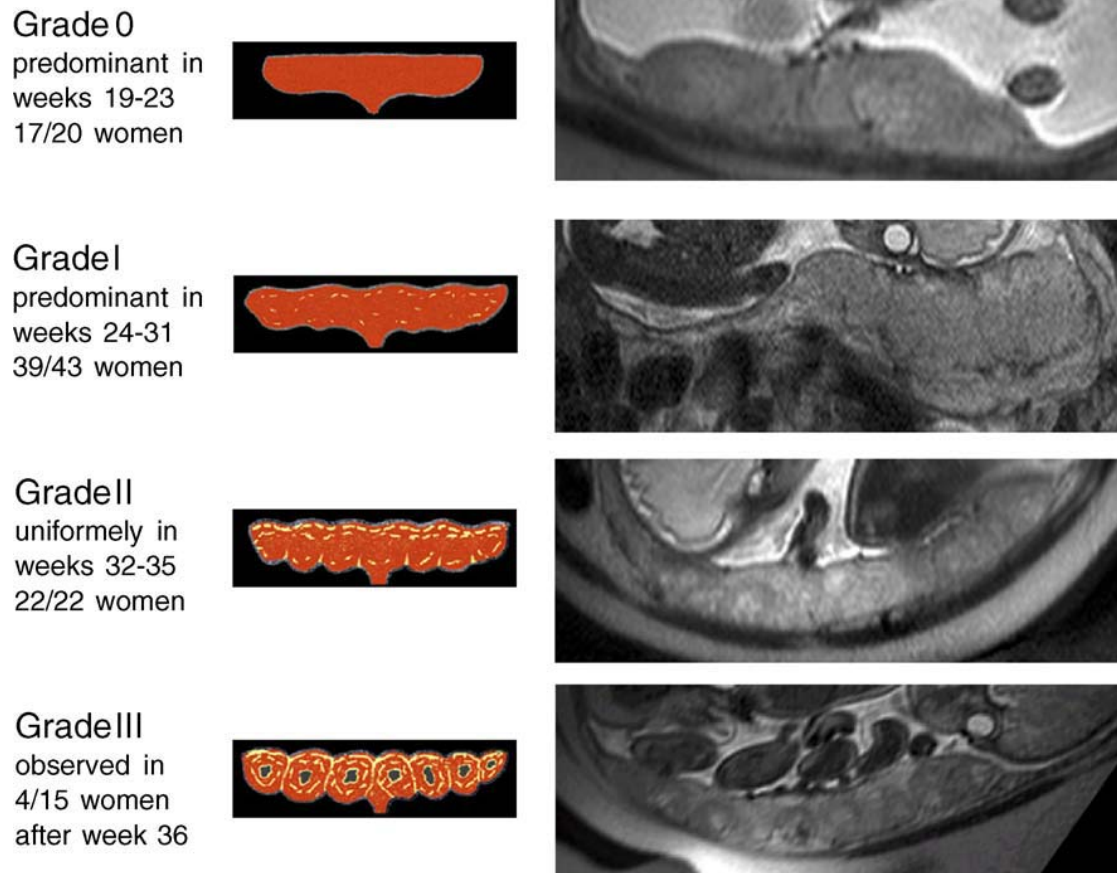


Fig. 1. Changes in placental appearance during gestation on MRI.

Fig. 2. Development of placental grading with ongoing gestation.

courtesy : W. Blaicher et al. / European Journal of Radiology .

showed a negative correlation with gestation. [p =0. 01 and 0.03 respectively] They conclude that T1 and T2 signal intensity measurements are influenced by changes in placental structure and may be fibrin dependant. Drawback of the study was the less number [only 30] of placentas evaluated.

Few authors have tried to correlate MRI appearance of the placenta with histopathological changes. In 2009 N. Linduska et al³² studied 45 placentas between 19-35 week. They found Placental hemorrhages [retro placental hematoma, intervillous thrombi and sub chorionic hematoma] and infarcts caused signal intensity changes on MRI while chorioamnionitis and massive perivillous fibrin deposition showed few signal intensity changes.

Damodaran et al³³ studied 20 growth restricted and 28 normal fetuses to identify a placental phenotype by MRI to predict fetal or neonatal mortality. They studied placental volume, placental thickness, thickness to volume ratio, placenta to amniotic fluid signal intensity ratio and abnormal signal intensity in placenta. They found that IUGR placentas had a globular thick appearance, an increase in placental thickness to volume ratio and a significant increase in volume of placenta affected by pathology. The presence of the first two parameters also had

an increased incidence of fetal or neonatal mortality [p=0.001 and p<0.001 respectively]

Diffusion weighted imaging of the placenta was found promising to diagnose IUGR by Harold Macel Bonel et al.³⁴. They found ADC values was $177.1 \text{ sec/mm}^2 \pm 18.90$ in normal fetuses versus $146.4 \text{ sec/mm}^2 \pm 10.63$ for fetuses with placental insufficiency. P values were <01. They conclude that a decreased ADC could be used as an early marker of placental damage.

Placental perfusion has been studied in many ways. Due to possible adverse effects of the contrast media on the vulnerable fetus these studies have been restricted to research, or have been done for other indications and not for direct assessment of placental perfusion. The mean placental perfusion values in various studies^{35,36} ranged from 176-209 ml/min/100ml of tissue in normal placentas to 139 ml/min/100ml in IUGR placentas. Brunelli et al³⁷ studied placental flow dynamics in 14 IUGR placentas referred for a contrast study to rule out placental adhesion. They found IUGR placentas had a significant amount of underperfused areas as compared to normal placentas.

Although no teratogenicity and no effect on postnatal development have been proved, the use of contrast media to study the placenta still remains controversial.

PATIENTS AND METHODS

PATIENTS AND METHODS

This prospective, quantitative, observational, case control study was carried out between June 2012 and July 2015 at Government General Hospital, Madras Medical College. Approval for the study was obtained from Madras Medical College Ethical Review Committee. Written maternal consent was obtained from individual mothers before inclusion in the study.

Sample Population:

With a prevalence of 5-10% of IUGR pregnancies, minimum sample size was estimated at 76. Antenatal Mothers referred for an ultrasound or Doppler screening to the radiology department for various indications, were screened by ultrasound and recruited for the study.

Inclusion criteria:

1. Singleton Antenatal mothers with fetuses above 20 weeks gestational age referred for ultrasound and Doppler.
2. Diabetes and hypertensive antenatal mothers were included.
3. Antenatal mothers referred for MRI evaluation of the placenta.

Exclusion criteria.

1. First trimester pregnancies.
2. Antenatal mothers with fetuses with congenital anomalies.
3. Multiple pregnancies.
4. Claustrophobic patients.
5. Patients with known contraindications to MRI.

The study has two parts. The first was a prospective comparison of ultrasound, Doppler and MRI characteristics of the placenta and its blood flow. The second was a retrospective analysis of the signal intensity measurements on the collected data. [Fig - 13]

All patients underwent ultrasound and Doppler screening by Siemens Antares ultrasound machine. Ultrasound and Doppler were performed by Radiologist A with more than 10 years experience with the modality. An MRI was obtained within 1-2 days of Ultrasound evaluation on a Magnetom 1.5 Tesla Siemens equipment. Six of the antenatal mothers were screened using 3 Tesla Siemens Skyra machine. MRI parameters were evaluated by Radiologist B with more than 5 years experience in MRI who was blinded to the Outcome of the Ultrasound findings. Parameters as depicted in Fig-13 were assessed for individual

FIG : 13. : METHODOLOGY



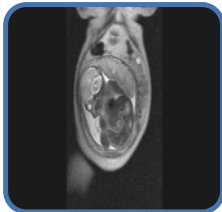
ultrasound

- Fetal age in weeks.
- Estimated fetal weight
- Placental appearance. grading, volume.
- Liquor volume.



Doppler

- Umbilical artery .
- Middle cerebral artery .
- Right uterine artery.
- IntraPlacental artery.
- Retro Placental artery



MRI

- T2 W axial , coronal and sagital images of uterus.
- T1W axial .

mothers. Based on estimated fetal weight and gestational age, they were categorized as normal or Intra Uterine growth restricted fetuses.

Ultrasound evaluation of estimated fetal weight was done by the machine based on Hadlock measurements. The amniotic fluid index was calculated using measurements from deepest pockets of all four quadrants of maternal abdomen. Placental volume was calculated by software on the machine, by three measurements obtained from largest placental diameter on axial and Sagittal images and thickness at site of the cord insertion on axial image.

The Umbilical artery readings were obtained from a free loop of cord. MCA readings were obtained just distal to its origin from Internal Carotid artery and UTA readings just distal to cross over by Iliac vessels.

Two Retro placental arterial tracings were obtained on either ends of placental insertion with suitable angle correction. Intra placental flow readings were obtained after angle correction on axial images of the placenta. Blood vessels were chosen on two sides, at a minimum of 1 cm from placental edge to ensure intraparenchymal readings. Average of measurements obtained was calculated.

Data Analysis:

Ultrasound biometric evaluation of fetus aided in calculating estimated fetal weight to categorize fetuses. Ultrasound of Placental size, placental volume, grade, appearance and Liquor volume was done. Doppler indices, including Peak systolic flow, End diastolic flow, Systolic /Diastolic ratio, Resistive indices [RI], Pulsatility indices [PI] of the Right Uterine artery, Umbilical artery, Middle Cerebral artery, Retroplacental and Intraplacental arteries was recorded. Cerebro placental ratio [CPR] of Pulsatility Index of Middle Cerebral Artery [MCA] versus Umbilical artery [UA] were calculated. Presence of diastolic notch in right Uterine Artery [UTA] was studied.

MRI images of placenta were evaluated for volume by measuring three longest dimensions on Axial and Sagittal images with thickness measured at the site of Umbilical cord insertion on axial images. The placental appearance was evaluated for heterogeneity and the presence of hypo intense areas. Signal intensity measurements of placenta were obtained as an average of three readings, on T1 and T2 weighted images, by placing three circular Regions of Interest [ROI] on the axial slice in which placenta had the largest diameter. [Fig- 14] Signal intensity measurements of Amniotic fluid were calculated as an average of three readings on T2 Weighted images. ROI's were placed in deepest amniotic

SIGNAL INTENSITY MEASUREMENTS BY MRI

Fig 14 – Placenta

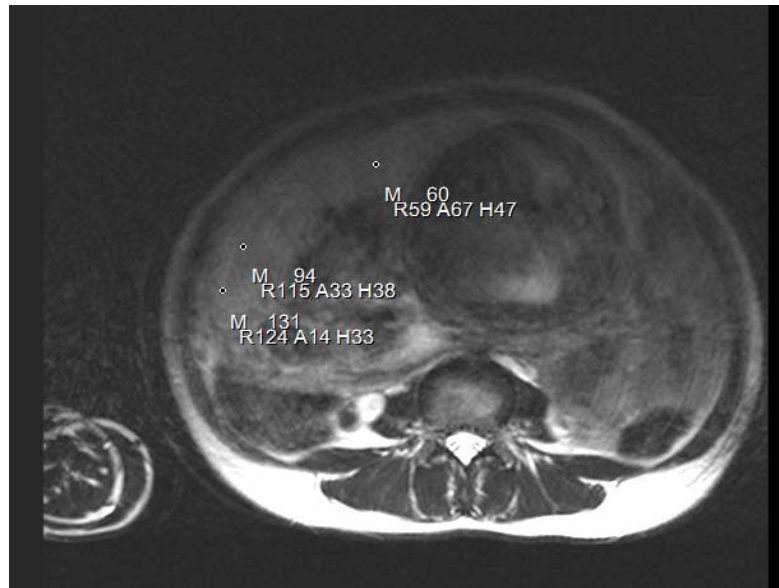
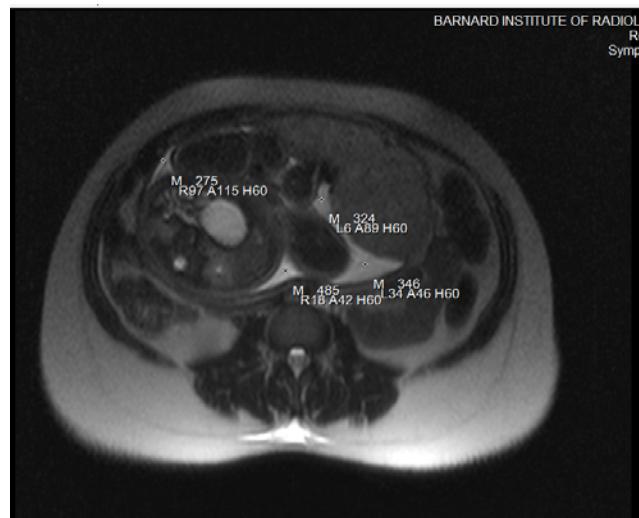


FIG -15 - AMNIOTIC FLUID



fluid pockets, preferably on a single axial slice [Fig-15], or if liquor was reduced, in adjacent axial slices with good pockets. Gluteus Maximus signal intensity was measured on T2 weighted images an average of four readings taken on a single axial slice with good muscle bulk. Roi's were placed two on the right and two on the left side of medial and lateral aspect of muscle mass. Fetal liver signal intensity was taken as an average of three readings obtained on a T2 weighted axial slice with maximum liver parenchyma.

From the signal intensity values on T2 weighted images of Placenta [PL], amniotic fluid [AF], Gluteus Maximus [GM] and Fetal liver [LIV]], following ratios were calculated AF/PL, LIV/PL, GM/PL, AF/GM, LIV/GM, PL/AF, PL/LIV and LIV/AF.

RESULTS AND ANALYSIS:

RESULTS AND ANALYSIS

159 singleton antenatal mothers with ages ranging from 18 to 38 years underwent ultrasound screening for estimation of gestational weight. A total of 98 growth restricted fetuses and 61 normal fetuses were screened.[Table -5].

TABLE 5- Categorisation of Antenatal mothers based on Fetal weight and Gestational Age at time of Ultrasound screening.

CATEGORY	A <5% IUGR			B 5- < 10 % IUGR			> 10 % Normal		
GROUPS	0	1	2	0	1	2	0	1	2-
WEEKS	<29	29-34	>34	<29	29-34	>34	<29	.29-34	>34
NUMBER	0	16	58	2	8	14	4	16	41
TOTAL	74			24			61		
GRAND TOTAL	159								
GROUP WISE TOTAL	<29 weeks = 6. 29-34 weeks = 40 > 34weeks = 113								

According to gestational weight all fetuses were placed under three categories. There were 74 pregnancies in Category A with severe IUGR [Intra uterine growth restriction] i.e. less than 5th percentile of expected gestational weight, 24 in Category B with mild IUGR i.e. between 5th -10th percentile of expected gestational weight and 61 with normal growth i.e. above the 10th percentile of gestational weight in Category C.

Further sub grouping was done based on gestational age at the time of ultrasound. Group 1- premature presentation, i.e. less than 29 weeks, Group 2 -early presentation, i.e. between 29 to 34 weeks and Group 3-late presentation i.e. between 34 weeks to term. When grouped according to gestational age 6 pregnancies belonged to less than 29weeks. 40 pregnancies were scanned between 29-34 weeks and 113 pregnancies in late gestation of above 34 weeks. [TABLE 5]

Effect of maternal causes like hypertension, diabetes, cardiac and renal illnesses, maternal anaemia and bad obstetric history on fetal growth restriction was studied. Hypertension was present in 18 /159 mothers. [11.3% prevalence] of whom 12 mothers had IUGR babies. [8 belonged to less than 5th percentile category and 4 to less than 10th percentile category]. Of the 18 with hypertension 6 mothers had fetuses with normal growth. Maternal diabetes was present in 17/159 [10.6%] mothers. Of them 5 [6.8%] belonged to Category A [less than 5th percentile IUGR fetuses] and 2 belonged to Category B [less than 10th percentile IUGR fetuses]. Out of these 10 belonged to category C [i.e. above the 10th percentile expected weight].

Apart from Diabetes and Hypertension, associated medical illnesses like abuminuria, cardiac diseases, anemia, renal disorders or history of treatment for infertility was present in 41 [26 %] of the

mothers included in the study group. Of these in 41 mothers with associated medical illnesses or history, the prevalence of medical illnesses was as follows- albuminuria [5/159-3%], cardiac disease [14/159-8.8%], bad obstetric history [19/159-11.9%], anemia [1/159 - 0.6%], and a history of infertility treatment [2/158 -1.25 %]. There was an overwhelming correlation between the incidence of IUGR in mothers with diabetes [p- .0001] or medical illnesses [p-. 006] in Category A [less than 5th percentile IUGR] and moderate correlation [p-. 044] in occurrence of IUGR in mothers with diabetes in Category B [less than 10th percentile IUGR].

USG grading of placenta, according to Grannums classification was done in 156 pregnancies, 6 in Subgroup -1 [less than 29 weeks], 39 in subgroup -2 [between 29-34 weeks] and 111 in Subgroup -3 [above 34 weeks gestational age]. In Subgroup -2 fetuses, 81.2 % of Category -C fetuses were grade 1 or 2, while 82.6% of Category -A or Category -B fetuses were grade 2 or 3. In Subgroup -3, 97.5% of Category -C fetuses were associated with grade 2 or 3 placentas while 95.7% of IUGR Category A or Category - B fetuses had placental grades of 2 or 3.

Placentas were grouped based on overall ultrasound appearance, presence of cysts and appearance of cotyledons. The 6 groups were homogenous appearance [Group1], heterogenous appearance [Group2],

cysts with thin margins [Group 3], cysts with echogenic margins [Group 4], hyper echoic cotyledons [Group 5] and sub chorionic hemorrhage [Group 6]. Cysts were common in both IUGR and normal placentas but cysts with echogenic margins [Group 4] were seen more frequently in IUGR [33/94] placentas as compared to normal placentas [10/70] of Group 1. Homogenous appearance was common in mature placentas while hyper echoic cotyledons [Group- 5] were seen in 5/35 [17%] of normal placentas and in 5/94 [5%] of IUGR placentas. Sub chorionic hemorrhage was seen in one mother. The sensitivity and specificity of cysts with echogenic margins in IUGR was 35% and 85% respectively. The Positive predictive value and odds ratio was 0.76 and 3.3 respectively. The sensitivity, specificity, Positive Predictive value and Odds Ratio were 5%, 87%, 0.5 and 0.4 respectively for echogenic cotyledons.

Placental volume was assessed by Ultrasound in 158 placentas. Based on Ultrasound volume, [Table - 6] Placentas were grouped into 6 groups as less than 200 cm³ [Group 1], 200-400cm³ [Group 2], 400-600cm³ [Group 3], 400-600cm³ [Group 4], 600-800cm³ [Group 5], and above 800cm³ [Group 6]. There were 6 mothers in gestational Sub group- 1 [less than 29 weeks], 39 in gestational Sub group-2 [29-34 weeks] and 113 in gestational Subgroup- 3 [above 34 weeks]

TABLE -6.Grouping by placental volume.

PLAC volume	Group 0 <29 weeks			Group 1			Group 2-above 34		
	5% iugr	5-10%	>10%	5%	5-10	>10%	5%	5-10%	>10 %
0-0-200 cm ³	-	1/50	1/25	5/31.3	2/25	3/18.8	14/24.1	4/28.6	5/12.2
1- 200-400	-	1/50	2/50	9/56.3	4/50	8/50	35/60.3	6/42.9	24/58.5
2-400-600	-	0	1/25	1/6.3	1/12.5	4/25	3/5.2	4/28.6	12/29.3
3-600-800	-	0	0	1/6.3	1/12.5	0	5/8.6	0	0
4- 800-1000	-	0	0	0	0	0	1/1.7	0	0
		2	4/100	16/100	8/100	15/100	58/100	14/100	41/100
Total	6			39			113		
	158								

Of the 6 patients screened in gestational Sub group- 1, 50% [1/2] of Category B IUGR fetuses and 50% [2/4] of Category - C normal fetuses fell into placental volume 200-400 cm³ levels.

In the 39 fetuses scanned in gestational Sub group-2, 54 % [9/16] in Category A and 50% [4/8] of Category B IUGR fetuses and 50% [8/15] of Category C normal fetuses had a placental weight of 200-400 grams cm³.

In the 113 fetuses scanned in Subgroup -3 , 56 % [41/72] of IUGR fetuses [Category A or B] and 58.5% [24/41] of Category -C normal fetuses had placental volume between 200-400 cm³, while [7/72] 9 % of IUGR fetuses [Category A or B] and [12/41] 29.3 % of Category -C

normal fetuses had placentas with volume between 400-600 cm³. Mild significance was found in the placental volume between Category A IUGR placentas [. 055], Category B IUGR placentas [. 013] and normal Category C placentas. Sensitivity, Specificity, Positive Predictive value and Odds Ratio were as follows – 56%, 41%, 0.63 and 0.93 respectively.

Presence of calcification in the placenta was graded 0 to 3 as Grade - 0 [no calcification], Grade -1 [specks of calcification], Grade - 2 [basal calcification] and Grade -3 [calcification of the cotyledons]. In gestational Subgroup -1 or 2, 81% [13/16] of Category -C normal placentas had no calcification and belonged to Grade 0, less than 18% [3/16] had calcification and belonged to other Grades. In comparison, in the IUGR group [Category A or Category B] 45 % [10/22] had no calcification [Grade 0] and 54 % [12/22] showed calcification [Other Grades].

In the above 34 weeks gestational age group, 27 % [11/40] of placentas in Category -C fetuses, had no calcification [Grade 0], while 72 % [29/40] of them had basal or cotyledon calcification [Grade 2 &3]. In the IUGR group [Category A or B] 20% [14 /69] had no calcification [Grade 0], and 79% [55/69] had calcification. Of those in the IUGR group with calcification, 59% [41/69] had minimum calcification [Grade -1] and 20% [14/69] had extensive cotyledon calcification [Grade -3]. The

sensitivity, specificity, Positive Predictive value and Odds Ratio were 16%, 9%, 0.66 and 1.33 respectively.

Doppler values calculated were Peak Systolic Velocity [PSV], End Diastolic Velocity [EDV], Resistive Index [RI], Pulsatility index [PI], and Systolic /Diastolic ratio [S/D] of Middle Cerebral artery [MCA], Umbilical artery [UA], Right Uterine artery [UTA], Intraplacental vessels and Retro placental vessels.

Abnormal Umbilical artery waveform was found in 4/157 in Category -A IUGR fetuses. In gestational age Subgroup -2 , 6.3 % [1/16] had absent end diastole and 6.3% [1/16] had reversed diastole. In gestational age Subgroup -3 , 3.4% [2/58] had reversed diastole. Normal waveforms were noted in 91% of Category B and 100 % of Category C fetuses. Therefore abnormal Umbilical waveforms were reliable in severe IUGR.

Uterine artery notching was found in 14% [22/151] of pregnant women. With Subgroup -1 gestational age, it was prevalent in 16 % [1/6], Subgroup -2 prevalence was 18 % [7/37] and in Subgroup -3 incidence was 11% [12/108]. Occurrence in IUGR fetuses was as follows: 18 % [13/71] belonged to Category -A, 25% [6/24] to Category- B and less than 5% [3/56] to Category -C normal gestation.

TABLE 7: Statistical Significance of mean Doppler values between IUGR categories

Parameter	Mean		P value
	>10% NORMAL [61]	<10% IUGR [24]	
UA PI	1.1	2.3	0.003
IPLPSV	19.3	23.7	0.02
IPL S/D	1.8	2.9	0.03
MCA RI	0.75	3.7	0.001
	>10% Normal [n= 61]	< 5% IUGR [n=74]	
MCA PI	2.06	1.5	.04
RPL PI	1.68	0.65	.05
IPL PSV	19.3	18.4	.02
IPL EDV	11.3	9.5	.01

Comparing mean values of doppler indices [Table 7] between IUGR Category -B and normal Category -C fetuses moderate statistical significance was found for UA PI, IPL PSV and overwhelming significance for IPL S/D. Between Category -A IUGR fetuses and normal Category C fetuses, moderate significance was found for MCA PI, RPL PI, IPL PSV and IPL EDV.

Comparing IUGR between gestational age groups [Table 10] statistical significance was overwhelming [i.e. Less than.001] for Umbilical artery PI [. 001] and IPL S/D [. 001]. Strong statistical significance was found for MCA RI and IPL PSV [. 02].

TABLE 8: Statistical Significance of mean Doppler values between IUGR categories with respect to Gestational age:

Parameter	Group 0 <29 weeks			Group 1			Group 2-above 34			P Value
	5% iugr	<10 %	>10 %	5%	5-10	>10%	5%	5-10%	>10 %	
MCA RI	-	0.69	0.77	0.76	9.6	0.7	0.73	0.77	0.76	0.01
UA PI	-	14.0	1.2	1.29	1.47	1.0	1.19	1.1	1.1	0.001
IPL PSV	-	20.3	14.6	17.0	34.5	15.3	18.9	18.0	21.4	0.02
IPL S/D	-	1.7	2.2	1.9	4.9	1.5	2.01	1.9	1.8	0.001

MRI study was obtained for 137 placentas. Classified by the shape of placenta 111 placentas were disc shaped of which 63 were present in IUGR fetuses in Category -A [46] and Category -B [17]. Thin and elongated placentas were seen in 6 pregnancies, of which 4 belonged to IUGR Category -A and 2 to normal Category -C pregnancies. Globoid shape presented in 21 pregnancies, of which 12 [57%] belonged to Category -A IUGR, 3 [14%] to Category -B IUGR and 6 [28%] to Category -C normal fetuses. Of the 15 globoid placentas presenting in IUGR fetuses, 5 [33%] presented in Subgroup -2 early IUGR, and 10 [66%] in late IUGR i.e. Subgroup- 3. p value for placental shape was .001 between Category A IUGR and Category C normal fetuses and .018 between Category-B IUGR and Category - C normal fetuses.

Artifacts distorted signal intensity measurements in 8 of the 137 patients for whom MRI was obtained. Based on signal intensity and

appearance on T2 weighted images 129 placentas were grouped into 7 Groups as homogenous and isointense [Group 0], homogenous and hyper intense [Group 1], homogenous and hypo intense [Group -2], heterogenous with hyper intense areas [Group- 3], heterogenous with hypo intense areas [Group - 4], heterogenous with hyper intense cotyledons [Group - 5] and heterogenous with hypo intense cotyledons [Group -6].

Of 129 placentas screened with MRI, 75 were IUGR placentas and 54 were normal placentas. There were 6 placentas in gestational age Subgroup -1, of which 4 were associated with normal fetuses. Of these four, 3 [75 %] were homogenous and isointense [Group -0] in appearance. Of the two IUGR placentas in Subgroup -1, one was isointense [Group-0]and one was heterogenous with hyper intense areas [Group -3].

In the gestational age Subgroup -2, 16 IUGR placentas and 15 normal placentas were screened. Of the latter 4 [26%] were homogenous and hypo intense in appearance [Group -2], 5 [33 %] were heterogenous with hyper intense area [group 3], 3 [20%] had hyper intense cotyledons [Group -5], 2 [13%] were heterointense with hypo intense areas [Group - 4] and 1 [6%] was homogenous and hypo intense [Group -2]. Of the 16 IUGR placentas 8 [50%] were heterointense with predominant hyper

intense areas [Group -3], 4 [25%] were homogenous and isointense [Group -0], 3 [18%] had hyper intense cotyledons [Group -5] and 1 [6%] was homogeneously hypo intense [Group -2].

92 placentas screened belonged to gestational age Subgroup - 2. [Above 34 weeks GA]. 35 were normal and 57 were IUGR placentas. Of the normal placentas 11 [31%] were heterogenous and hyper intense in appearance [Group -3], 8 [22%] were homogenous and isointense [Group -0], 6 [17%] had hyper intense cotyledons [Group -5], 5 [14%] were homogeneously hyper intense [Group -1], 4 [11%] were homogeneously hypo intense [Group -2], and 1 [2%] had hypo intense cotyledons [Group -6]. The 57 IUGR placentas in this group had signal intensity as follows. 26 [45%] were heterogenous with hyper intense areas [Group -3], 10 [17%] had hyper intense cotyledons [Group -5], 8 [14%] were homogenous and isointense [Group -0], 4 [7%] each were heterogenous with hypo intense areas [Group -3] and hypo intense cotyledons [Group -6], 3 [5%] were homogenous and hypo intense [Group -2], and 2 [3%] were homogeneously hyper intense [Group -1]. Presence of Hypo intensity in the placentas, either homogenous, or as hypo intense areas or hypo intense cotyledons as a predictor of placental fibrosis in IUGR fetuses had a sensitivity, specificity and Positive predictive value as 16%,

83% and 57% respectively. p value for placental appearance was .053 between Category A IUGR fetuses and Category C normal fetuses.





T1 and T2 Signal intensity values of the placenta and fetal liver in pregnancies with normal growth showed a decreasing trend with increasing gestational age. Amniotic fluid signal intensity on the other hand showed an increasing trend with gestational age. Within the gestational age group IUGR placentas showed increased T1 and T2 values as compared to normal placentas while AFI showed decreased values in IUGR placentas of the same gestational age group.

Across all age groups mean placental T1 was 68.7 for normal growth and raised to 81 in Category A IUGR fetuses and 106 in Category B IUGR fetuses. Average Placental T2 was 167 for normal placentas and was increased to 175 in both IUGR categories. Amniotic Fluid Index was 287 in Category C normal placentas and elevated to 364 in Category A IUGR fetuses and 300 in Category B IUGR fetuses. Mean values for normal fetal liver was 78.3 and elevated to 85.9 in Category A IUGR fetuses and to 79.7 in Category B IUGR fetuses.

Significant correlation was found for PL T1 [p -. 042] PL T2 [p-.036] and AF T2 [p -. 011] between Category C normal placentas and Category A IUGR placentas. LIV T2 value was significant [p- .043] between Category A normal fetuses and Category B IUGR fetuses.

MRI ratios available for 68 patients showed a decreasing trend as gestational age advanced for AF/PL, LIV /PL, GM/PL, PL/AF &LIV/AF ratios and an increasing trend for AF/GM, LIV/GM and PL/LIV.

**TABLE 9- TREND ON MEAN VALUE OF MRI RATIOS
ACROSS IUGR CATEGORIES**

IUGR CATEGORY	AF/PL N=68	LIV/PL 67	GM/PL 66	AF/GM 68	LIV/GM 67	PL/AF 68	PL/LIV 66	LIV/AF 69
Categ C >10th %tile	1.7	0.40	0.90	2.14	1.99	0.63	2.41	0.29
Categ B 5th -10th %tile	2.13	0.43	0.95	2.96	0.63	0.66	3.09	0.22
Categ A Less than 5th %tile	2.2	0.46	3.43	2.5	0.53	0.51	4.7	0.21
Trend normal to IUGR								

With reference to IUGR fetuses MR ratios [Table - 9] revealed an increasing trend for AF/PL, LIV /PL, GM /PL, AF/GM, and PL/LIV and a decreasing trend for LIV/GM, PL/AF and LIV/AF from Normal to IUGR fetuses. Significant correlation was found for AF/PL [p-. 003, mean value in Category C normal placentas was 1.7 & mean value for Category A IUGR placentas was 2.25] and for LIV/GM [p -. 043, mean values for Category C normal placentas was 1.99 & mean value for

Category A IUGR placentas was 0.53]. between Category A IUGR and Category C normal fetuses

Fetal outcome was classified into four types as A] normal outcome, [normal outcome or ICU admission of less than 1 week] B] mild morbidity [ICU admission less than 2 weeks or those with late preterm delivery] C] severe morbidity [more than 2 weeks ICU admission or early preterm delivery before 34 weeks gestational age] and D] Perinatal mortality.

Of the 146 fetuses with known outcome [Table 12],

- A] Normal outcome was noted in 107/142 fetuses. [75%].
- B] Mild morbidity was present in 23/142 [16%] fetuses, 14 admitted for less than 2 weeks and 9 who were delivered late preterm.
- C] Severe morbidity in 5/142 [0.03%] was due to 2 admitted in ICU for more than 2 weeks and 3 who were early preterm deliveries.
- D] Fetal mortality was noted in total of 11 fetuses.

A significant correlation was noted for some of the parameters as in Table 10.

High risk indicators in IUGR fetuses:

- 1] H/o of Co. morbidities like maternal medical illnesses other than hypertension or Diabetes was significantly [p-.0001] associated with fetal morbidity mortality outcome. Diabetes [p-. 047] showed a mild association.
- 2] Of the Doppler parameters high significance was noted for UA EDV [. 0001], UA RI [. 0001], UA S/D [. 0001], Absent EDV in UA [. 008], UTA RI [. 0001] and RPL PSV [. 015]
- 3]. A significant correlation was noted for the following MRI parameters. Placental T2signal intensity [. 001] and placental type [. 004] showed high significance while Placental T2/AF ratio showed moderate significance [. 015]. Mild significance was noted in shape [. 035] and AF/GM ratio [. 024].

DISCUSSION:

DISCUSSION

Intrauterine growth restriction is a condition where the growing fetus is unable to achieve its inherent growth potential. All fetuses have an inherent growth potential based on the genes they inherit. Some of these fetuses are not able to reach the predestined level of growth due to causes which may be environmental or maternal. All fetuses with an estimated weight below the 10th percentile are small for gestational age. Of these some fetuses are constitutionally small while others fall into the category of IUGR.

Fetal growth restriction is one of the most challenging obstetric problems. Due to confusing terminology like small for gestational age and intrauterine growth restriction with no clear cut differentiation between the two and no uniform diagnostic criteria for IUGR whether less than 10th, 5th or 3rd percentile the very identification of IUGR fetuses becomes a diagnostic dilemma.

The first step in the management of IUGR [FIG-16] is to differentiate between fetuses that are truly IUGR and at risk for adverse outcomes versus small fetuses that are normal in stature and those in whom the underlying condition will not alter with treatment. [E.g., aneuploidy, syndromes, viral infections]. Therefore, prior to imaging, a

**Fig - 16 DIAGNOSTIC ALGORITHM FOR
WORK UP IN IUGR FETUSES**

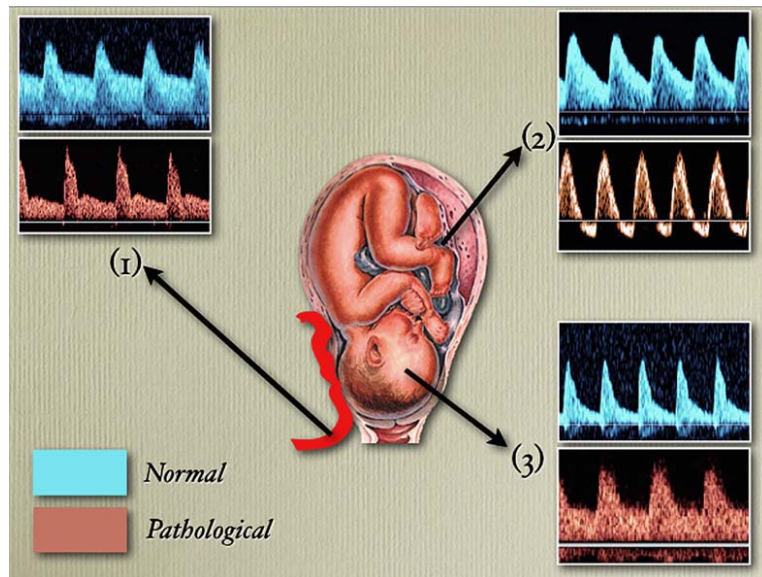
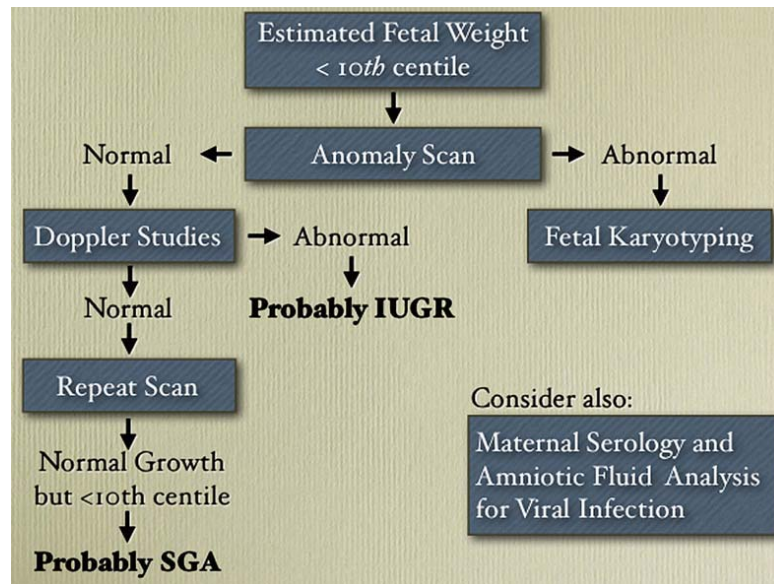


FIG 16 - - Normal and pathological uterine artery (1), umbilical arterial (2) and middle cerebral artery (3) Doppler waveforms. A compromised fetus will show a uterine artery waveform with ‘notching’, a reverse flow in the umbilical artery waveform and an increased diastolic component in the middle cerebral artery.

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detailed history and clinical examination is necessary to exclude hypertension, renal disorders, coagulation profiles etc.

The first indicator of possible IUGR is based on estimation of the abdominal circumference or fetal weight estimation. IUGR may be defined as an estimated fetal weight below the 10th percentile. Asymmetry of the HC/AC ratio suggests altered growth dynamics. Once small for date gestational fetuses are identified those among them prone for adverse outcomes have to be identified. This is done based on imaging studies. The combination of biometry with Umbilical artery and Middle Cerebral artery Doppler studies provides the best tool to identify the fetus at risk for adverse outcome.³⁸ Randomized trials have confirmed the validity of Umbilical artery Doppler in reduction of Perinatal mortality.¹⁹ Once suspicion of IUGR is confirmed, further evaluation to identify underlying pathology like Coagulation defects, infective causes etc should be undertaken. Once these are ruled out antenatal surveillance should be started based on severity of maternal or fetal condition.

There was a significant association of diabetes [p-. 0001] and maternal medical conditions [. 006] with the occurrence of IUGR. Hypertension, Diabetes and Medical causes had a causative role in early onset IUGR. In late onset IUGR Hypertension and medical conditions had a more definitive role than Diabetes.

Traditionally ultrasound was used to evaluate the fetus than the placenta. Initially it was used just to locate the placenta to rule out interference during delivery or for invasion of myometrium which could cause Post partum haemorrhage. Later on the placenta was evaluated for inherent pathologies and to shed some light on growth retardation. The normal placental appearance varies with gestational age. At initial gestational stages the placenta is uniform in echogenicity and discoid in shape. Normal thickness at cord insertion is 2 to 4 cm.³⁹ The placenta can be thinner in Systemic diseases, vascular and hematologic diseases which could cause micro infarctions .Thicker placentas are imaged in fetal hydrops, maternal diabetes and maternal anaemia.

As gestation advances it assumes a more lobulated appearance with scattered echogenicity and calcification. Grading of placenta [Fig 8] attempted in 1973 initially as a method of predicting lung maturity¹⁵ was later used for detecting IUGR.⁴⁰ Grading of Placenta showed poor correlation with IUGR in my study as in previous studies.

Maturation of the is accompanied by appearance of cysts. In IUGR placentas, normal invasion of the smooth muscle of the spiral arteries does not occur, and therefore the spiral arteries constantly deliver a forceful jet of blood into the intervillous space. This constant force causes blunting of villi and erosion, with formation of cystic spaces which may

later on get thrombosed. Therefore formation of increased number of cystic spaces indicates high resistance flow in the placenta. Most of these cystic or hypo echoic areas represent placental lakes filled with slow flowing maternal blood.³⁹ They are normally seen unless associated with decreased Umbilical artery flow when they can be associated with fetal growth restriction.⁴¹ Intervillous thrombus forms due to fetal hemorrhage that rapidly thrombose, in the intervillous space. These intervillous thrombi are usually less than 1-2 cm in size. Thrombi larger than 3cm may be associated with placental disease. Cysts with echogenic margins indicate intervillous thrombus while solid echogenic areas denote villous infarcts. In this study cysts were common in both normal and IUGR placentas. Cysts with echogenic margins [Fig 17] representing intervillous thrombus with no flow, was more common in IUGR placentas [35% occurrence in IUGR as compared to 14 % in normal placentas]. But the Sensitivity and Specificity of this finding to denote IUGR placentas was low. [35% and 85% respectively]. Cysts with echogenic margins were more frequently seen in IUGR placentas with gestational age above 34 weeks [42%] as compared to less than 34 weeks [12.5%]. However, there was no statistical significance.

Placental volume was found to have significant correlation [$p > 0.5$] with IUGR in previous studies, but in this study there was no significant

FIG -17: PLACENTAL ULTRASOUND. -ECHOGENIC CYST



Echogenic cyst in Placenta of third trimester fetus with IUGR of less than 5th percentile.

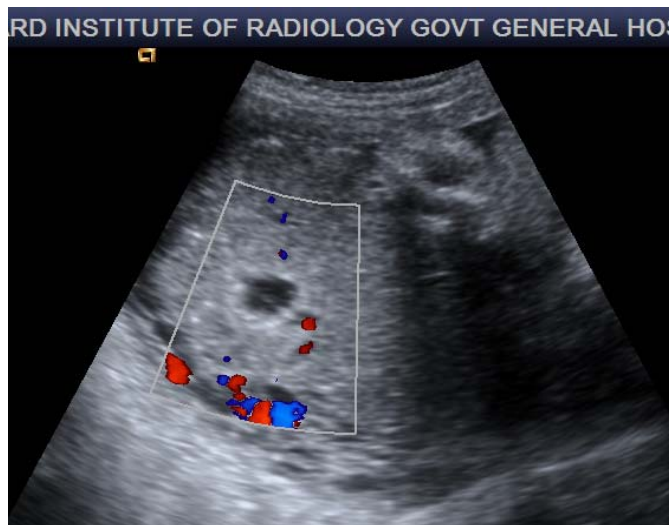
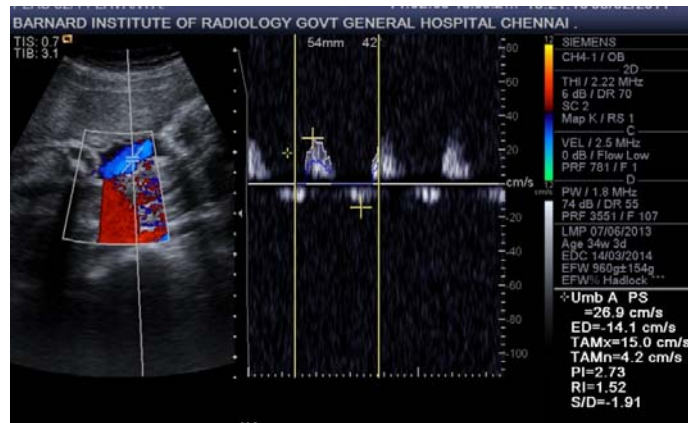
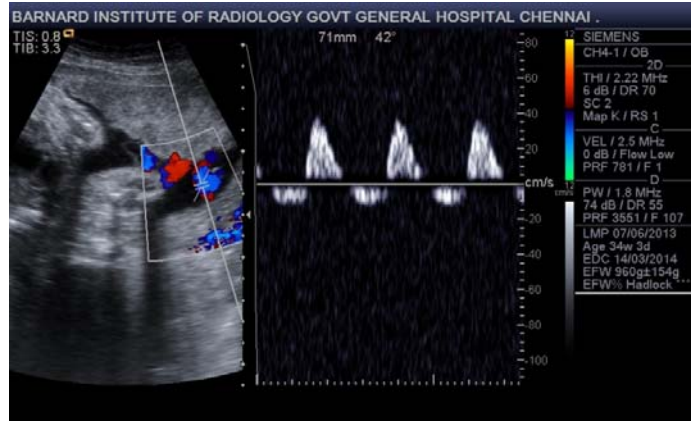


Fig 17.- Same cyst with no flow on doppler representing intervillous thrombosis

correlation. It may be due to the fact that volume estimation was done on 2D images as compared to volume estimation by 3D which may give a more actual measurement. Similarly, there was no significant difference in grade of calcification between normal and IUGR placentas. Calcification prior to 34 weeks was however more common in IUGR than normal placentas. [54% versus 18%].

In normal pregnancies the Resistive index [RI], Pulsatility index [PI] and Systolic /Diastolic [S/D] ratio in the Umbilical artery should decrease with advancing gestational age. To the contrary, it has been established by various studies that the decreased diastolic flow caused by increased resistance in the placental bed, increases the RI, PI and S/D ratios in growth restricted fetuses. As placental insufficiency worsens the waveform progresses to absent and then reversed diastolic flow in the Umbilical artery. Absent or Reversed End Diastolic flow in the Umbilical artery are predictors of adverse Perinatal outcome. The prevalence of Perinatal death in these fetuses has been found to be more than 40 %. Of the 4 mothers with abnormal umbilical artery waveforms the three who had reversed diastole [FIG - 18] presented with severe IUGR below the 5th percentile, while absent end diastolic flow was noted in mild IUGR [i.e between 5th to 10th percentile weight group]. All fetuses with abnormal Umbilical artery waveforms died in the Perinatal period. The PI

**FIG 18 : UMBILICAL ARTERY REVERSED END
DIASTOLIC FLOW. [UA REDF]**



ID - 52/14.

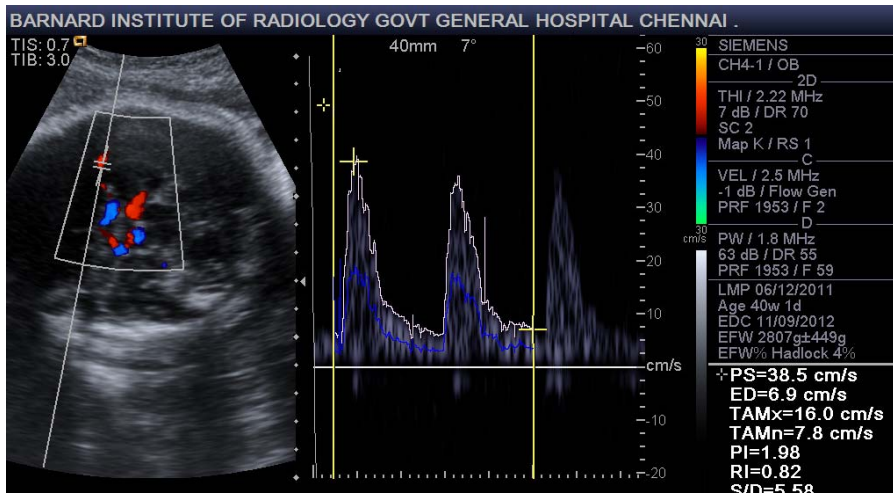
INVESTIGATIONS: Urine protein +

IUGR: < 5% IUGR

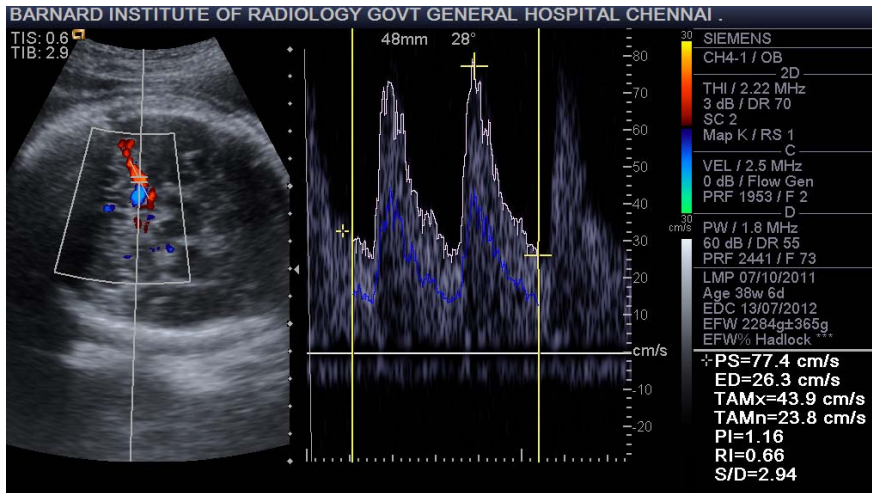
DOPPLER: UA reversal . PI- 2.7. RI-1.5.

OUTCOME : fetus died in Utero.

**FIG 19: MCA [MIDDLE CEREBRAL ARTERIAL]
FLOW IN NORMAL AND IUGR FETUSES**



**FIG 19 A- High resistance MCA flow in normal fetus.MCA PI is 1.98.
[ID No-17] Cerebro placental ratio -1.6**



**FIG 19 B- Brain sparing effect in IUGR fetus, [1D No 8].MCA PI is 1.16.
Cerebro placental ratio -1.**

of umbilical artery was found highly significant in predicting IUGR between normal and less than 10th percentile IUGR. [Table 7]

Fetal Middle cerebral artery [MCA] is a low resistance circulation throughout pregnancy. The normal fetus responds to chronic hypoxia by redistributing the blood flow to essential organs like heart, kidneys and brain depicted by increased diastolic flow in Middle cerebral artery; and vasoconstriction to other intraabdominal organs. This results in asymmetric growth restriction. Due to cerebral vasodilatation the diastolic flow in cerebral vessels increase, causing the low Pulsatility index in Middle cerebral artery. [Fig -19]. Therefore the Cerebro placental ratio of the Pulsatility index falls to below 1.08.⁴² Increased diastolic flow with decreased Pulsatility indicates the brain sparing effect. A cerebral placental ratio [i.e. Pulsatility index of MCA by PI of Umbilical artery] less than 1 indicates fetal compromise.

The fetal descending aorta also shows changes in placental insufficiency. In this study no statistical significance was found for the Cerebro Placental ratio [CP Ratio] between IUGR and normal groups, unlike other studies, but moderate significance was found in MCA PI [.04] between normal and less than 5% IUGR. This correlates with an earlier Indian study by Lakhar et al²² who found greater sensitivity for

the MCA PI as compared to the CP ratio in predicting adverse Perinatal outcome.

By hypothesis the placenta is the seat of insufficiency and Doppler evaluation of Intraplacental blood flow should reflect pathologic changes in the placental bed. Therefore, two additional vessels studied were the Intraplacental arteries [Fig 20] and Retro placental arteries[Fig 21] . Peak systolic velocity, end diastolic velocity, Resistive index, Pulsatility index and Systolic Diastolic ratio were calculated. Of these great statistical significance was found in Intra placental S/D [-001] and moderate significance of IPL PSV [. 02] and IPL EDV [. 01]. These parameters therefore gave additional input over the PI of Umbilical artery.

Comparing Doppler between gestational age groups, the overwhelming statistical significance was found for UA PI [$<.001$] and IPL S/D [. 001]. Strong statistical significance was associated with MCA RI and IPL PSV [. 02].

PLACENTAL IMAGING BY MRI

There are various changes that take place in the placenta in IUGR fetuses. These may be in the form of morphological large lesions like cysts which can be picked up by ultrasound. But many a times these changes take place on a microscopic level, such as maldevelopment of

**FIG 20:INTRAPALACENTAL FLOW[IPL]
IN NORMAL AND IUGR FETUSES**

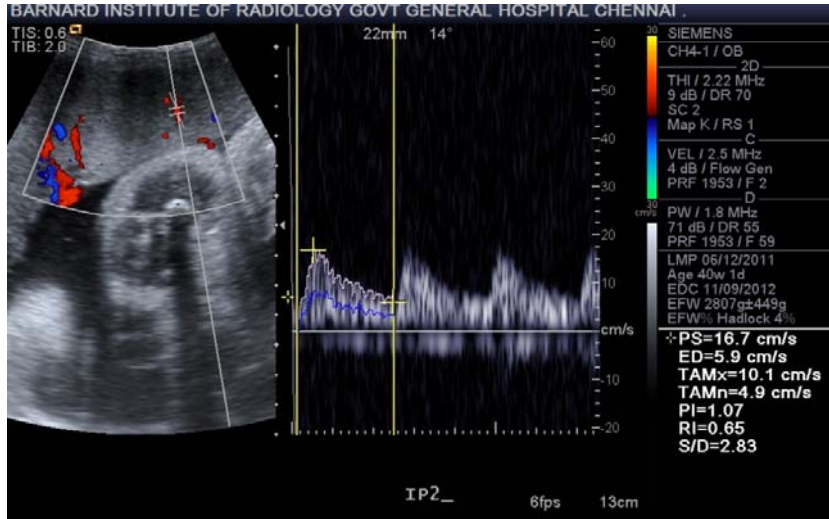


FIG 20A - Normal fetus.

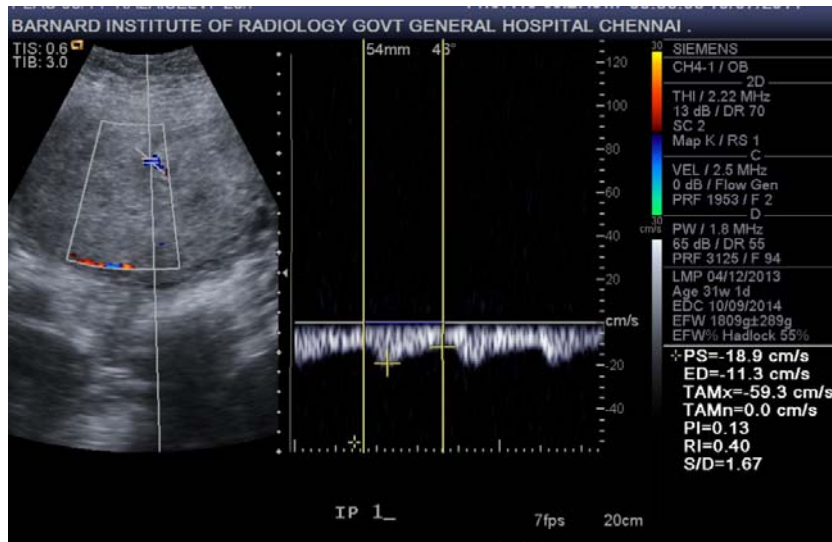
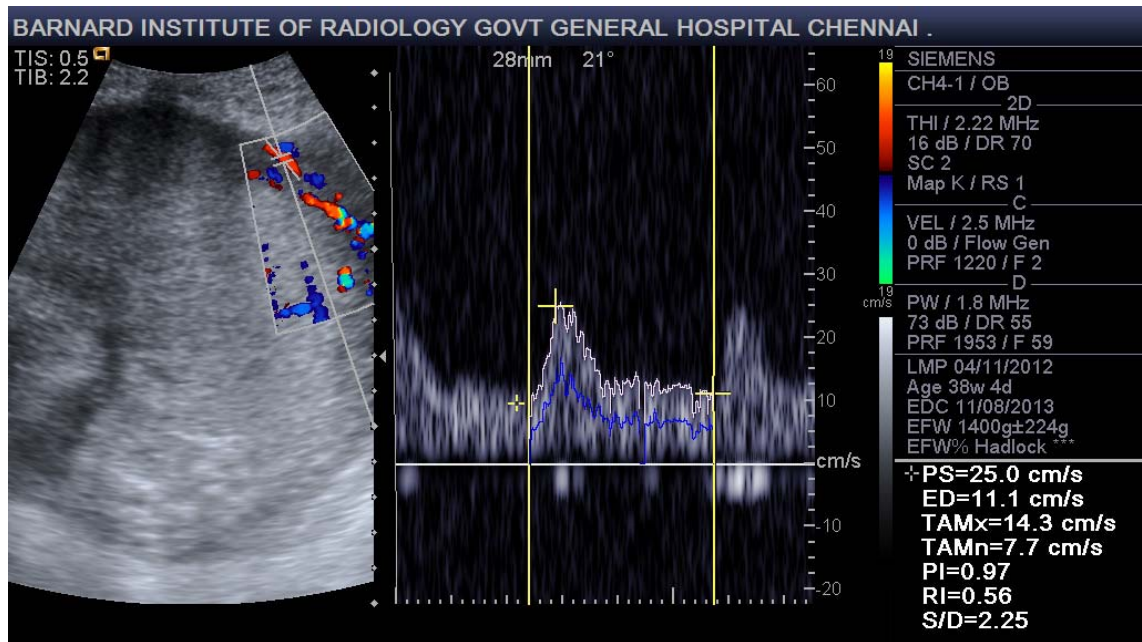


Fig 20 B – IUGR Fetus.

FIG 21 - RETRO PLACENTAL FLOW IN IUGR FETUS



ID NO - 31/ 14.

HISTORY: --nil relevant.

29 -34 weeks.

Early Asymmetric IUGR. <5th percentile Category.

USG:No calcification, AFI -5,

DOPPLER

UTA: Uterine artery notch present. PI of uterine artery =normal.

UA: normal.

IPL - S/D =2.1,

RPL PI = 0.97.

OUTCOME : Fetus died in utero 20 days after caesarean.

villi, changes in thickness and surface area of the placental exchange membranes etc. These changes are not visible on routine ultrasound. Microscopic changes may, however cause effects on Doppler, if large areas of the placenta are involved, but by and large go undetected by imaging until IUGR sets in. These morphologic and physiologic changes in the placenta may form a placental phenotype in IUGR. This phenotype if detected early by imaging studies can aid in the early detection and management of IUGR.

MRI can provide various qualitative and quantitative indices to evaluate the placenta. At the gross level, MRI can detect changes in placental thickness and volume in normal versus IUGR pregnancies. Image contrast in MRI depends on differences in tissue relaxation times between various tissues. Though it is not known specifically what histopathology in the placenta causes these changes in relaxation times, studies have revealed that water content and membrane surface area had an important influence on relaxation times.

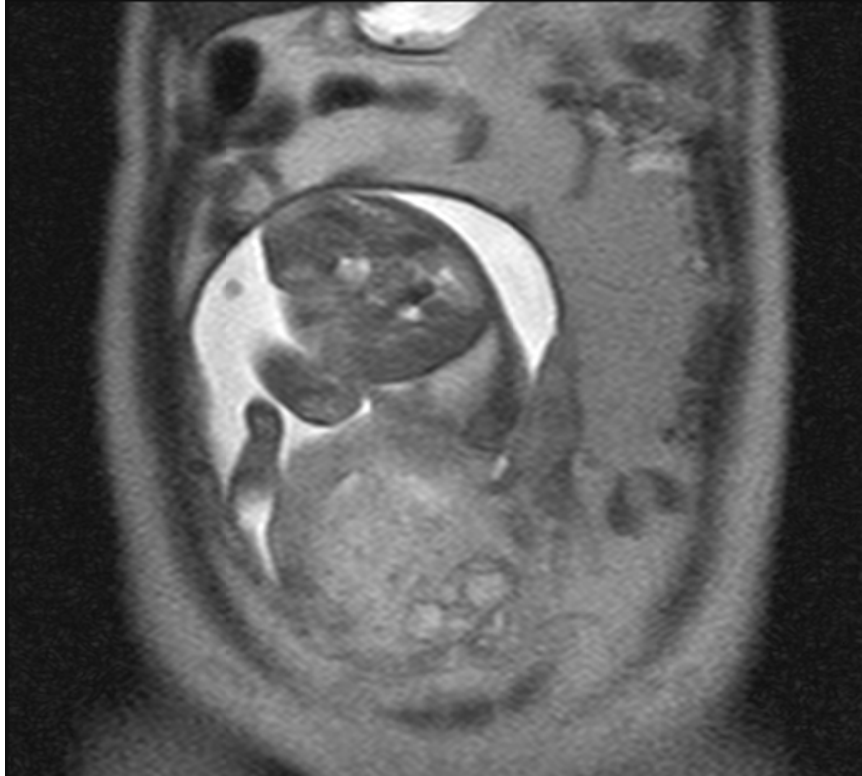
There are very few articles describing the imaging findings in normal placenta by MRI. Most studies have concentrated on normal placental morphology confirming the discoid shape, Placental thickness at cord of between 2-4 cm and uniform signal intensity.

The placenta is well seen on MRI with its superior contrast resolution and fixed location as compared to the moving fetus. The

normal placenta is intermediate in signal intensity with a hypo intense band separating the decidual surface from underlying myometrium.³⁹ It is normally discoid in shape. Grading of the normal placenta by MRI has been attempted similar to Ultrasound grading, as a sign of placental maturity³⁰. With advancing gestational age similar to changes on ultrasound the appearance of lobulated contour and more heterointense appearance on T2 [fig - 12] can be appreciated on Placental MRI. T1 images were not useful to study normal placental appearance as they were mostly uniform in appearance across all age groups. However T1 weighted images are useful to identify placental vascular abnormalities such as infarcts, sub chorionic hemorrhage and intervillous haemorrhages⁴³ that appear hyper intense. Placental signal intensities on T2 weighted images have been recorded. The placental/ amniotic fluid signal ratio [PL/AF ratio] decreases with advancing gestational age³⁰. This may reflect the morphological changes occurring in the placenta with maturation.

In IUGR the placenta acquires a globular shape,³³ [Fig-22] with increased thickness and reduced volume. This correlated with the significance of placental shape with IUGR in this study. The globular appearance of placenta was highly significant [. 001] between normal and less than 5th percentile IUGR and moderately significant [. 018] between

FIG 22 : GLOBULAR PLACENTA IN IUGR PREGNANCY WITH MIXED INTENSE LESION – HAEMORRHAGIC INFARCT



Normal and less than 10th percentile IUGR. No correlation with placental volume was noted. This may be due to calculation of volume based on three measurements of length, breadth and thickness rather than a total of actual measurements per slice.

Hypo intense areas in the placenta could correspond to fibrotic replacement of placental tissue³¹. Hypo intense areas had a mild significance with the presence of IUGR in this study.

The T1 and T2 signal intensities of a normal placenta showed a gradual decline with increasing gestational age [Fig -23]. This in accordance with earlier studies^{31,33}. The amniotic fluid signal intensity and fetal liver were not studied in previous studies. The AF showed an increasing value with advancing gestational age probably due to increased cellular content as gestation advances. Fetal liver showed a decreasing trend with gestational age. Within the same age group IUGR placentas revealed a higher intensity values for T1 and T2 reflecting the early maturation as seen by increased calcification and cystic villous lakes on ultrasound of IUGR placentas. Moderately significant correlation was found for T1, T2 and AFI values between Normal and IUGR placentas.

Other than estimation of placenta to amniotic fluid signal intensity ratio, other ratios pertaining to MRI of the placenta have not been

FIG -23A: T2 WEIGHTED NORMAL DISC SHAPED HOMOGENOUS PLACENTA IN EARLY PREGNANCY

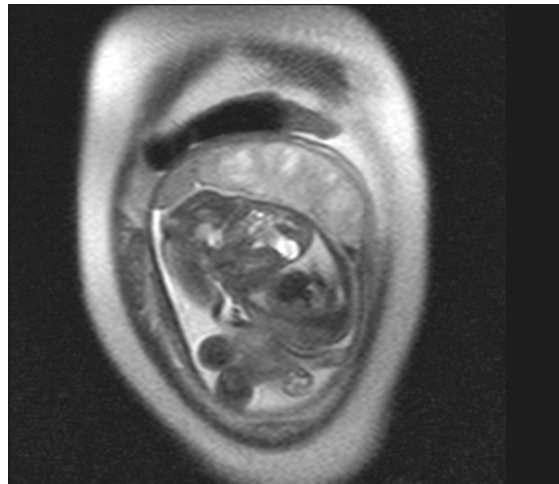
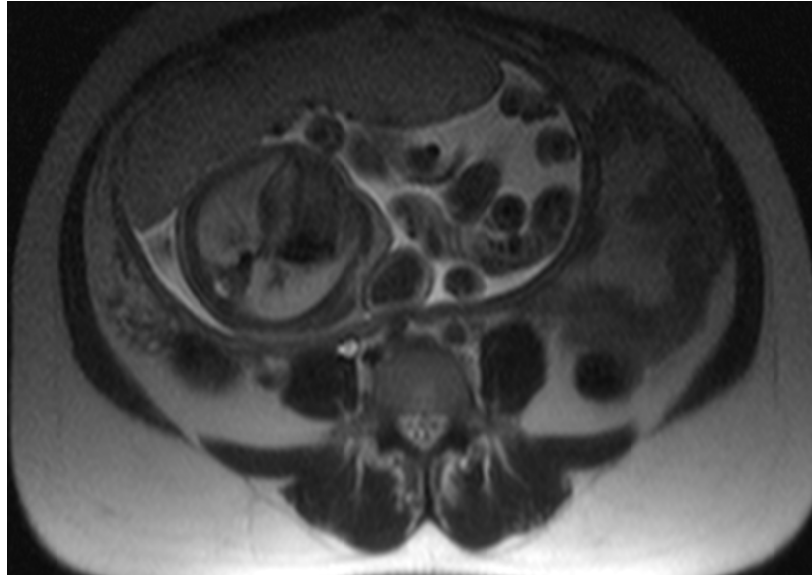




FIG 23B: T2 weighed image of heterointense term placenta.


assessed previously. The signal intensity of Gluteus Maximus was taken as a standard value not affected by IUGR. Of the ratios estimated there was a significant difference in AF/PL, and LIV /GM values between normal and less than 5th percentile IUGR fetuses. These ratios may therefore be used after proper validation to differentiate between severe IUGR and small for date fetuses.


**TABLE 10- SIGNIFICANT IMAGING PARAMETERS
COMPARED TO MORBIDITY AND MORTALITY**

PARAM	SIGN P-	0 [82] Normal [a]	1 [25] 1 day ICU [a]	2 [10] < 7 days [b]	3 [4] 7-14 days [b]	4 [9] Late Preterm [b]	5 [2] > 14 days [c]	6 [3] Early preterm [c]	7 [7] Death [d]
MEDICAL	.0001								
DIAB	.047								
DOPPLER									
UA EDV	.0001	19.5	7.6	16.8	9.1	13.5	13.4	17	7.8
UA RI	.0001	.63	.65	.67	.76	.68	.69	.71	.85
UA S/D	.0001	3.0	3.2	3.6	4.3	3.4	3.6	7.4	6.4
UT RI	.0001	.52	.50	.51	.59	.54	.63	1.2	.57
Abs EDV	.008								
RPL PSV	.015	44.4	39.7	62.2	70.1	43.8	45.6	41.0	46.7
MCA EDV	.043	13.8	11.8	36.7	13.1	12.1	14.8	12.2	15.9
MRI									
PL T2	.001	186	189	174	175	180	412	267	246
TYPE	.004								
PL/AF	.015	.59	.56	.56	.39	.54	.48	1.2	.58
AF/GM	.024	2.4	2.2	2.4	4.2	2.7	5.4	2.1	2.7
SHAPE	.035								

 0&1
NO MORBIDITY.

 2, 3 &4
MILD MORBIDITY

 5 &6
SEVERE MORBIDITY

 7
MORTALITY

INDICATORS OF FETAL MORTALITY AND MORBIDITY

1. Maternal health plays an important part in fetal well being. Especially maternal medical conditions like hypertension, thyroid dysfunction, cardiac disorders and preeclampsia had a greater effect on fetal growth than diabetes which had a mild association with IUGR. This may also be due to the predominant finding of milder rather than severe diabetes in the study group and due to lower number of mothers with diabetes in the group studied.
2. Doppler parameters indicative of morbidity were UA EDV, UA RI, UA S/D, absent EDV, and RPL PSV. Therefore the umbilical artery indices were all useful in predicting morbidity, and also the newly evaluated retro placental flow a reflection of the uterine flow.
3. Of the MRI parameters placental T2, Placental appearance, PL/AF ratio, AF/GM ratio, and placental shape had significance in predicting mortality and morbidity.
4. Comparing between perinatal fetal mortality and live deliveries significant correlation was found for PL T1 and AF/PL ratio.

Surveillance of High Risk Fetuses

Surveillance of the high risk fetus should be individualized for each fetus depending on maternal and fetal condition and gestational age at presentation. Primary surveillance tools include Fetal heart rate analysis, Doppler ultrasound, Amniotic fluid assessment and fetal biophysical profile assessment.

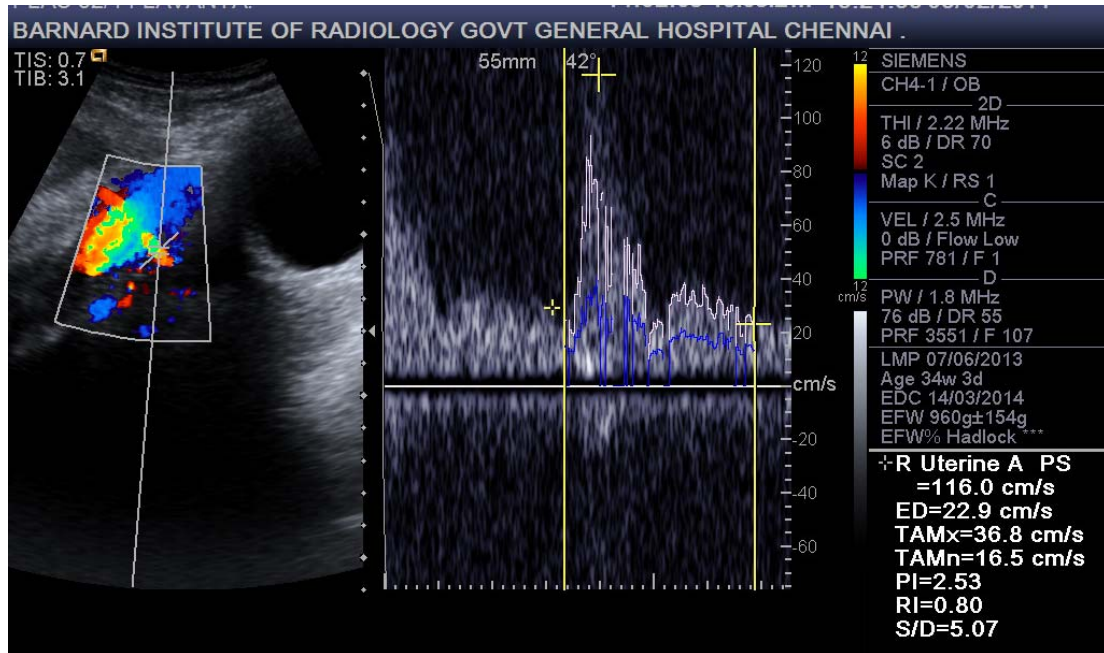
Uterine artery Doppler [Fig - 24] is useful in high risk pregnancies as a screening tool. At 18-22 weeks in high risk mothers with pre-eclampsia a mean PI value > 1.45 has a sensitivity of over 70% for the detection of IUGR.

MANAGEMENT OF IUGR:

The first step is to detect the presence of IUGR in the growing fetus.

- 1] **Biometry:** The identification of IUGR fetus is based on Biometry. The Abdominal circumference estimation is the best single determinant of fetal size and weight. Absence of growth as judged by Biometry over a period of two weeks detects IUGR. Once detected by fetal Biometry FGR [Fetal growth Restriction] fetuses are placed in high Risk Surveillance group.

FIG 24- DIASTOLIC NOTCHING IN UTERINE ARTERY WITH RAISED PI



ID NO - 52/14.

HISTORY: --Trace albumin in urine.

32-33weeks

Early Asymmetric IUGR. <5 th percentile Category.

USG: No calcification, AFI -7.

DOPPLER

UTA: Uterine artery notch present. PI of uterine artery =2.5.[normal < 1.45]

UA: Reversed Diastole.

OUTCOME : Fetus died in utero 2 days after scan.

- 2] Cardio topography: is a form of fetal assessment to record the fetal heart rate, movements and Uterine contractions. Variations in heart rate and episodic accelerations are indicative of normal brain functioning ⁴⁴. In hypoxic FGR the fetal heart rate is faster and has lower baseline variation.
- 3] Biophysical Profile [BPP] and Amniotic Fluid volume: This was developed as a method to assess fetal well being. But by the time, BPP becomes abnormal, the decreasing fetal tone, fetal movements and reduced liquor are indicative of severe fetal acidosis and renal failure. The very aim of delivering a fetus in good condition is thus not met if the delivery is planned only after an abnormal BPP. Thus, it has a limited role in fetal surveillance.
- 4] Doppler Analysis: Routine Doppler in low risk or unselected population is not beneficial. It is however a very useful tool in high risk pregnancies. Abnormal Umbilical artery waveforms indicate poor placental function. On the venous side abnormal ductus venosus tracings indicates more advanced stage of adaptation to placental insufficiency.
- 5] MRI: the role of MRI is yet to be established in high risk surveillance. Currently it can be used as an adjunct to Ultrasound.

The routine use of MRI is inhibited by its cost, availability and still to be established role in antenatal surveillance.

Timing of delivery: Currently there is no clear cut protocol, or medicines that can help in treating IUGR. Most treatments are individualized to the particular patient. Thrombolytic drugs, steroids, etc. have been tried. But the only realistic course is the timing of delivery. The time of delivery is chosen balancing the risk of fetal intrapartum mortality if delivery is delayed, with the benefits of an extended stay in the intra uterine safe environment with increasing lung and organ maturity.

When a growth retarded fetus is found to have normal tests of fetal well being, the fetus is placed under increased surveillance until delivery at term. It is rare for subsequent deterioration to occur as the primary cause of growth retardation would not have been placental insufficiency⁴⁴.

If the Doppler parameters are abnormal the risk of too early delivery and neonatal death has to be balanced with prolonged intrapartum exposure to fetal hypoxia and acidosis that can result in brain damage or death. Therefore, it is important to know the sequence of changes in fetal Doppler.⁴⁵ The first abnormalities detected are Amniotic fluid index and UA PI, followed by MCA and Aortic Doppler changes. Variations in cardio topography occur, followed by abnormalities in

venous Doppler of Ductus venosus and Inferior vena cava. Arterial Doppler changes occur 4 weeks before delivery while Venous changes become abnormal 1 week before, according to various studies.

TABLE 10 - Comparison of Early and late onset IUGR

EARLY IUGR [BEFORE 34 WEEKS]	LATE IUGR AFTER 34 WEEKS
Rare	Common [80 %]
Easy to diagnose	Difficult to diagnose.
Severe placental insufficiency	Mild Placental insufficiency.
Abnormal umbilical artery doppler	Usually normal umbilical artery Doppler.
Brain redistribution of flow [depicted by increasing MCA PI] usually occurs early and therefore not useful for clinical management	Brain redistribution occurs later and crucial for decision making.
High perinatal mortality and severe long term morbidity.	Low perinatal mortality. High long term morbidity.
Fetal tolerance high	Fetal tolerance low. Large number of still births.
Management challenge	Diagnostic challenge

If abnormal Doppler findings occur prior to 32 weeks, i.e. in early onset IUGR[Table 10], additional markers of decompensation like echogenic bowel, cardiomegaly, abnormal ductus venosus waveform and abnormal cardio topography [short term variation of fetal heart rate] are looked for. If these markers are present, delivery by caesarean section after administration of steroids is the best option for the fetus. If growth retardation is the late onset type, abnormal Doppler tracings especially Umbilical artery absent end diastolic flow it can be an indication for prompt delivery⁴⁶. The Middle Cerebral artery Doppler is especially useful to predict brain sparing effect.[Table 10]

FUTURE PREGNANCIES:

IUGR can recur in future pregnancies.The risk of recurrence depends on the etiology.It is dependant on the underlying cause as well as the maternal health and co morbidities.

Therefore a pathological study of the IUGR placenta will aid in locating the underlying cause of placental insufficiency, which may aid in management of subsequent pregnancies. Severe placental insufficiency has a 10 % risk of recurrence in otherwise healthy women.

Risk of recurrence is increased in

- Persistent chronic hypertension
- Advanced maternal age

- Maternal kidney or autoimmune disease
- Maternal clotting disorders
- Maternal obesity
- Certain long term medications of the mother

These women should be enrolled in high risk surveillance by imaging. It needs to be studied if MRI parameters would aid in this aspect.

SUMMARY & CONCLUSION

SUMMARY & CONCLUSION

Fetal growth restriction is one of the most challenging problems in obstetrics. It is detrimental to the health of both mother and baby. It is well known that neonates who have not reached their growth potential in utero, are at increased risk to health throughout their life. It is also complicated by the fact that there are no clear cut diagnostic criteria to differentiate IUGR fetuses from small for gestational age, but normal fetuses. Lack of differentiation, will result in unwanted premature delivery of otherwise normal small for date fetuses. This may cause undue stress to both mother and fetus, who would have otherwise had a normal outcome.

Accurate diagnosis and management of intrauterine growth restriction depends on a combination of tests

- To accurately date the pregnancy by early fetal Biometry.
- To assess intrauterine growth curve by regular Biometry and identify IUGR fetuses.
- Among IUGR fetuses to identify high risk pregnancies and place them under close surveillance.
- To choose an appropriate time to deliver the fetus with minimal risk to mother and baby.

This study emphasizes the value of imaging studies, especially Doppler and MR indices that indicate a risk to the fetus. Stated in order of importance they are :

- i. High on the list of indices to predict high risk to the fetus are the Umbilical artery Resistive index, UA Systolic / Diastolic ratio and End Diastolic velocity in the Umbilical artery . Uterine artery Resistive index and maternal Co- morbidities like Hypertension, Renal disorders and anemia were also significant high risk indicators.
- ii. Moderately significant risk indicators were MR parameters of Placental T2 signal intensity measurements and placental appearance. Also significant, were Absent or reversed end diastolic flow in Umbilical artery and Retroplacental arterial Peak Systolic velocity. Of the MR ratios evaluated PL /AF and AF/GM ratios were predictive of increased morbidity to the fetus.
- iii. Of lesser significance as risk indicators were shape of placenta by MRI and Middle Cerebral artery end diastole volume. The least significant risk indicator was maternal diabetes.

MR imaging may be superior to US in some settings, owing to improved soft-tissue contrast and wider field of view; however, it is limited by cost, patient claustrophobia, and limited availability of technology and skilled image interpretation. MRI is superior to US in terms of limiting conditions that may impair sonography, like

oligohydramnios, obesity, adverse fetal position or posterior placed placenta. In case of unclear diagnosis on US, MRI is a perfect complement that increases the confidence and diagnostic accuracy of prenatal diagnosis.

There is now growing evidence of the value of MR in imaging and evaluation of fetal growth restriction. MR has been found useful to diagnose the presence of IUGR, predict the occurrence of fetal morbidity in fetal growth restriction and detect abnormalities in brain development of the IUGR fetus.

This study has added knowledge to the existing data regarding imaging of placenta by Doppler and MRI. Additional evaluation of Retroplacental and Intraplacental arteries has been found promising in IUGR. Regarding MRI new data about decreasing signal intensity of fetal liver with gestational age is exciting. The liver, the site of glycogen storage in healthy foetuses was found to be affected in IUGR foetuses as shown by significant correlation of AF/LIV ratios.

This study gives an Indian perspective to the appearance of normal MR placental appearance at various gestational ages and its comparison with fetal growth restriction. High risk indicators for ultrasound, Doppler and MRI have been evaluated. The significance of placental signal intensity measurements and the derived ratios have been established in the analysis of perinatal mortality and morbidity. This data may be used as a reference for future studies.

*IMPACT OF STUDY,LIMITATIONS
AND RECOMMENDATIONS*

IMPACT OF STUDY, LIMITATIONS AND RECOMMENDATIONS:

Although to researchers the importance of the placenta in fetal nutrition is obvious, in clinical obstetric imaging the fetus takes precedence. The placenta in obstetrics is always imaged as an afterthought.

This study proves the importance of placental imaging in High risk pregnancies and the role it plays in Intra uterine growth restriction. While currently Doppler takes precedence over all other modalities in assessing risk of perinatal morbidity and mortality it can only assess effects of placental insufficiency and does not provide information about the etiology.

This study proves that MRI with its excellent contrast resolution of the placenta can add insights to placental imaging. MRI gives additional information regarding placental fibrosis and the composition of the placenta. The shape and appearance of placenta on MRI and the signal intensity ratios can predict the occurrence of IUGR and impending morbidity. Changes in fetal liver with maturation of the fetus and its importance in IUGR has been seen.

Limitations of this study are the limited number of patients in each gestational age group, missing data and absence of biochemical and pathological correlation.

Future studies of MRI of the placenta should include a larger number of centers and patients. These results should be validated across different vendor machines. Diffusion weighted MR imaging of the placenta is also a promising tool. Radio - Pathological correlation would offer better insights about the placenta.

The placenta should be studied on 3 Tesla machines to evaluate for additional information . An interesting breakthrough would be to analyze the chemical composition of the placenta by spectroscopy, which can open up a new chapter in placental imaging.

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ABBREVIATION	EXPANSION
AFI	Amniotic Fluid Index
ADC	Apparent Diffusion Coefficient.
AEDV	Absent End Diastolic Flow in Umbilical artery.
BPP	Biophysical Profile
CPR	Cerebro Placental Ratio.
DAA	Descending Abdominal Aorta.
EDV	End Diastolic Velocity
FHR	Fetal Heart Tracing
GM	Gluteus Maximus.
IUGR	Intra Uterine fetal Growth Restriction.
IPL	Inraplacental
IVC	Inferior Vena Cava.
LIV	Fetal Liver
MCA	Middle Cerebral Artery.
MRI	Magnetic resonance Imaging.
PI	Pulsatility Index.
PSV	Peak Systolic Velocity
RI	Resistive Index
RPL	Retro Placental
ROI	Region Of Intrest.
SGA	Small for Gestational Age.
UA	Umbilical artery
UTA	Uterine Artery

RATIO	EXPANSION
AF/PL	Amniotic Fluid/ Placental T2.
AF/GM	Amniotic fluid/ Gluteus Maximus T2 intensities.
CPR	Cerebro Placental Ratio
HC/AC	Fetal head circumference / Abdominal Circumference
GM/PL	Gluteus Maximus /Placenta.
LIV/AF	Fetal liver / Amniotic fluid
LIV/GM	Fetal liver / Gluteus Maximus.
LIV/PL	Fetal Liver / Placental T2.
S/D	Systolic /Diastolic.

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INTRODUCTION

Normal fetal growth is an important component of a healthy pregnancy and influences the long term health of the offspring. Intra Uterine Fetal growth restriction [IUGR], previously known as Intrauterine Growth Retardation is defined as a rate of fetal growth that is less than normal for the growth potential of the fetus, for that particular gestational age. The fetus with IUGR fails to attain its genetically determined potential size.

The definition of IUGR usually refers to fetuses whose estimated birth weight is below the 10th percentile for its gestational age, whose abdominal circumference is below the 2.5th percentile (or) those whose birth weight at term is less than 2,500 Gms. While 80-85% of these fetuses are constitutionally small but healthy, 10-15% are true IUGR and the remaining 5-10% are affected by chromosomal or structural anomalies.¹ The fetal weight is determined by the



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